RENAL FUNCTION IN CHRONIC LIVER DISEASE

DISSERTATION SUBMITTED TO

THE TAMIL NADU DR.M.G.R MEDICAL

UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REGULATIONS

FOR THE AWARD OF THE DEGREE OF

M.D (GENERAL MEDICINE) BRANCH – I

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CERTIFICATE

This is to certify that the dissertation entitled "RENAL FUNCTION IN CHRONIC LIVER DISEASE" is the bonafide original work of Dr.DEEPIKA, in partial fulfillment of the requirements for M.D Branch-I (General Medicine) Examination of the Tamil Nadu Dr. M.G.R Medical University to be held in APRIL 2013.

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DECLARATION

I solemnly declare that the dissertation titled **"RENAL FUNCTION IN CHRONIC LIVER DISEASE"** was done by me at Tirunelveli Government Medical College and Hospital during 2011-2012 under the guidance and supervision of **PROF. DR. ARUMUGAPANDIAN @ MOHAN M.D.**, Professor of Medicine.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D DEGREE (BRANCH-I) in General Medicine.

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ABBREVIATION

NGAL - Neutrophil gelatinase associated lipocalin

RAAS - Renin Angiotensin Aldosterone System

HRS - Hepato renal syndrome

CrCl - Creatinine clearance

MARS - Molecular adsorbent recirculating system

GFR - Glomerular filtration rate.

PV - Peritoneo venous shunt

NAC - N –acetyl cysteine

TIPS - Transjugular intrahepatic portosystemic shunt

MELD - Model for End- Stage liver disease

k DA - kilo Dalton

AKI - Acute kidney Injury

KIM-1 - Kidney Injury Molecule -1

IL-18 - Interleukin -18

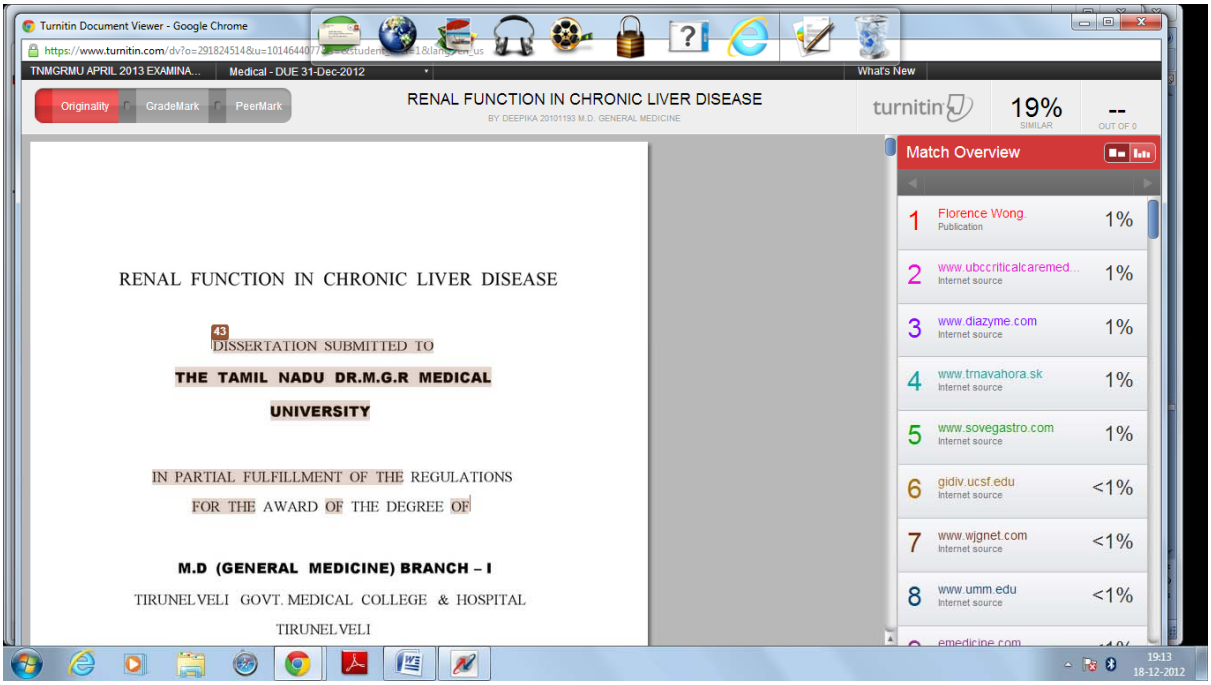
Osm - Osmolality

CVVH - Continuous veno venous filtration

CGF - Cockcroft Gault formula

PT - Prothrombin time

MDRD - Modification of diet in renal disease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CONTENTS

INTRODUCTION

Renal dysfunction is a frequent complication in cirrhotics and this combination has got a significant morbidity and mortality. Both liver and kidney disease can occur simultaneously or a primary liver disease can lead to secondary abnormalities in kidney function[1]

Decreased renal function in patients with cirrhosis is usually functional without any structural abnormality and occurs gradually over a period of time and has a negative impact on the prognosis of patients[2,3].

The incidence of renal failure in advanced chronic liver disease ranges from 15% to 50%[4].Patients with cirrhosis have circulatory dysfunction and diminished effective arterial volume leading to acute renal dysfunction in these patients. This acute kidney injury may be spontaneous or precipitated by infection , use of nephrotoxic drugs , blood loss or gastrointestinal fluid losses.

The accurate assessment of renal function is these patients is proving to be difficult due to excessive dependence on the plasma creatinine whose levels are dependent on various factors like the severity of chronic liver disease , malnutrition and elevated bilirubin levels which interferes with the estimation of serum creatinine.

Conventional biomarkers like blood urea , plasma creatinine and urine markers are non specific and insensitive for the detecting an acute decrease in renal function in these patients. Newer biomarkers for detecting renal injury are being evaluated in various studies. These include both serum and urine biomarkers namely serum neutrophil gelatinase associated lipocalin (sNGAL) and cystatin C. Urinary biomarkers include kidney injury molecule (KIM-1), NGAL (u NGAL) and interleukin -18 (IL-18)[5].

It is imperative to detect the onset, severity and progression of renal dysfunction in cirrhotics as this has got a major impact on the survival of these patients and is one of the major risk condition affecting the prognosis in patients undergoing liver transplantation .

Patients with pre transplant renal dysfunction are prone to develop complications than those without renal failure.

This emphasises the need for the earlier detection of renal dysfunction in cirrhotics for optimal management of these patients. This has prompted the evaluation of several biomarkers of renal injury like kidney injury molecule, serum and urine NGAL and cystatin C as markers of renal injury in these patients. Of these biomarkers Cystatin C has been studied the most in cirrhotics and it has been proved to be a superior marker to serum creatinine in this subgroup of patients.

AIMS

1. To evaluate the diagnostic accuracy of plasma creatinine and creatinine based formulas in assessing renal functions in patients with chronic liver disease

2. To assess the diagnostic accuracy of cystatin C and cystatin C based equations in assessing renal functions in chronic liver disease patients.

3. To find out whether etiology of chronic liver disease has an impact on renal function in these patients.

REVIEW OF LITERATURE

HISTORY :

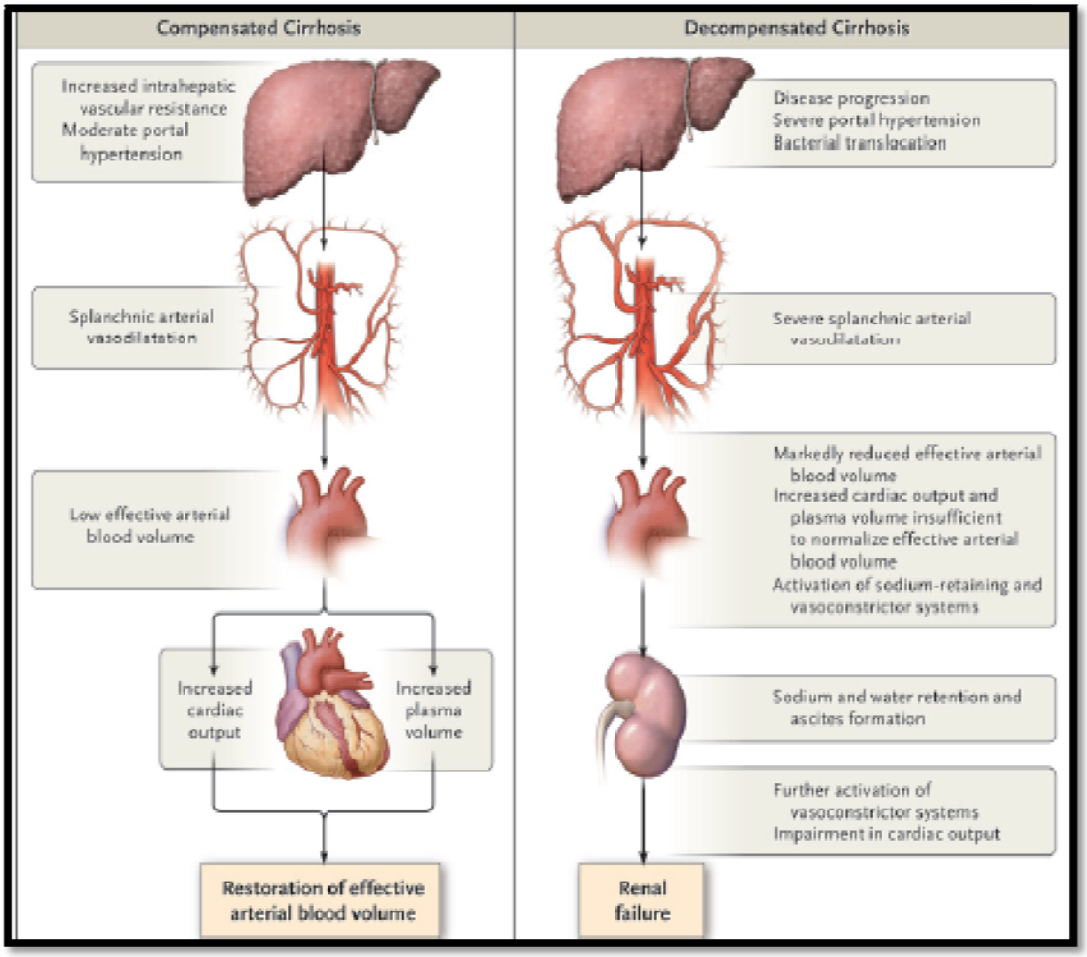
Frerich and Flint reported two cases of chronic liver disease with renal dysfunction in the late nineteenth century[6]. They described the occurrence of oliguria in cirrhotics in the absence of structural renal disease and proteinuria in these patients. Helwig and Schutz coined the term " Hepato renal syndrome" in 1932.

But it was Sherlock, Popper and Vessin in 1950 s who elaborated the functional nature of this syndrome and the occurrence of co existing systemic circulatory disturbances and its adverse impact on prognosis in the cirrhotics.

Further studies undertaken during the last two decades have shown that intense systemic arterial vasodilation in cirrhotics led to severe renal vasoconstriction which predisposed these patients to develop acute renal dysfunction, the most disastrous complication being the development of Hepatorenal syndrome.

PATHOPHYSIOLOGY OF RENAL DYSFUNCTION IN CIRRHOSIS:

The incidence of functional renal failure is estimated to be around 15% in cirrhotics with ascites and about 50% in patients who die. The risk of developing this complication in patients with ascites is estimated to be 30% and 40% at two and five years respectively and the renal failure is secondary to changes in systemic hemodynamics and renal perfusion, the kidneys themselves are otherwise normal.



The vicious cycle of renal failure starts with systemic circulatory disturbances . There is hyperdynamic circulation due to portal hypertension which results from scarring and fibrosis and architectural distortion of liver. Increased cardiac output and dilatation of peripheral vasculature is due to the release of endogenous compounds like nitric oxide[7] which are shunted from regional splanchnic to systemic circulation. Adrenomedullin, cannabinoids and carbon monoxide are other vasodilators causing systemic arterial vasodilatation leading to impaired effective arterial blood volume . Splanchnic circulation undergoes predominant vasodilatation where as renal vessels undergo relative vasoconstriction.[8]

The diminished effective arterial volume simulates a state of relative hypovolemia which leads to activation of compensatory mechanisms like the arginine vasopressin, sympathetic nervous system and RAAS [9,10] which try to conserve sodium levels in the body . Excessive sodium retention leads to fluid accumulation and ascites in these patients. Dilutional hyponatremia is a common complication of fluid retention in patients in advanced stages of liver disease. Severe and persistent activation of all these compensatory mechanisms leads to

constriction of extrasplanchnic vasculature in kidney leading to hepatorenal syndrome and in brain resulting in encephalopathy in these patients leading to multiorgan dysfunction .Intrarenal imbalance of vasodilatory compounds like prostaglandins, kallikreins and vasoconstrictors like endothelins[11 are postulated to be responsible for renal vasoconstriction

Renal arterial flow is maintained in the normal range during the earlier stages of hepatic disease and this may deteriorate suddenly if a 'second hit' occurs which may be in the form of gastrointestinal fluid losses leading to true hypovolemia in cirrhotics who are already at risk of developing renal failure. Persistent vasoconstriction leads to decrease in filtration of glomerular surface area resulting in ischemic acute tubular necrosis in these patients.

Acute renal failure can also be due to iatrogenic causes like use of nephrotoxic drugs like aminoglycosides, excessive fluid loss due to large volume and repeated abdominal paracentesis, blood loss . Renal dysfunction precipitated by infection usually resolves when the infection is being treated.

CAUSES OF RENAL FAILURE IN CIRRHOSIS :

In hospitalized patients with cirrhosis pre renal azotemia is the predominant cause of acute renal failure contributing to about 50 % . It is followed by acute tubular necrosis (30%) , hepatorenal syndrome (17%) and post renal failure (<1%)[12,13]

PRERENAL:

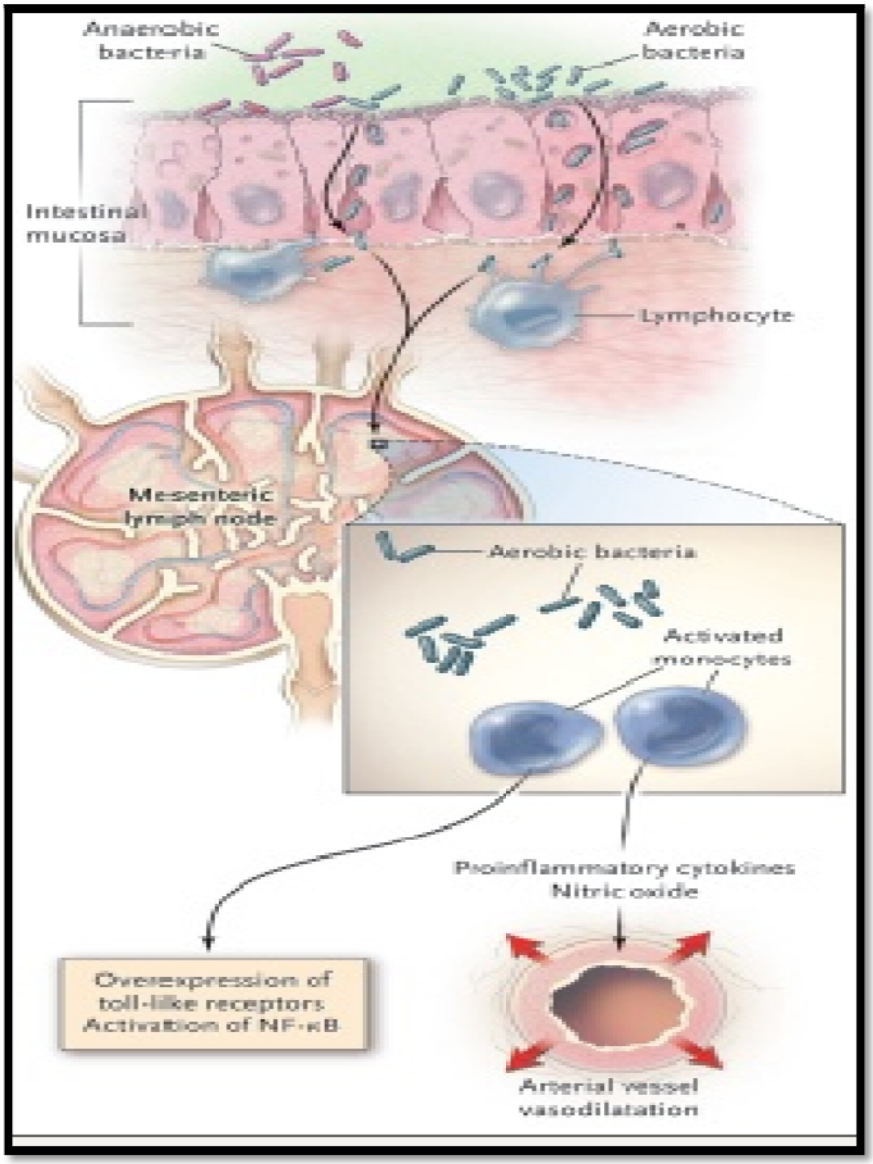
The persisting state of relative hypovolemia can be exacerbated by actual fluid loss like gastrointestinal fluid losses due to excessive vomiting and diarrhoea, blood loss due to variceal bleeding which occurs in portal hypertension or coagulation abnormalities which is one of the common complications in advanced decompensated liver disease or peptic ulcers causing a sudden drop in intravascular volume thus leading to prerenal azotemia.

Iatrogenic causes of prerenal azotemia include excessive use of diuretics, repeated and large volume abdominal paracentesis in the absence of adequate intravascular volume replacement. The use of non steroidal anti inflammatory drugs can exacerbate renal injury due to reduction of glomerular filtration pressure which initially results in prerenal azotemia but can progress to ischemic tubular necrosis if the injury persists.

Dimnished blood flow results in decreased supply of sodium to the macula densa resulting in activation of RAAS leading to ascites and fluid retention. Presence of refractory and tense ascites can further impair renal perfusion and contribute to renal injury.

Also cirrhotics are more prone for developing spontaneous bacterial peritonitis because of the low opsonizing capacity due to diminished complement activity. This occurs more when the total protein content of the ascitic fluid is less than one gram/ decilitre.

The most common cause of spontaneous bacterial peritonitis is the gram negative bacteria which translocate from the gut to the peritoneal cavity. Here they cause an inflammatory reaction leadingto the production of vaso active cytokines which causes circulatory dysfunction by causing vasodilation in systemic circulation and thereby diminishing the effective arterial circulation.



The presence of septic shock exacerbates renal injury further[14].

INTRINSIC RENAL FAILURE:

Acute tubular necrosis is the predominant cause of parenchymal renal injury in chronic liver disease patients .It is an extended spectrum of pre renal azotemia [15,16].It usually follows an episode of hypovolemic shock or after major surgical procedures causing volume loss in these patients. Other causes of intrinsic renal failure include the use of nephrotoxic agents like aminoglycosides or radiocontrast agents.

The decreased effective glomerular filtration pressure if prolonged , leads to dislodging of tubular epithelial cells from the basement membrane followed by occlusion of tubular lumen by cast cells leading to established acute renal failure in these patients.

Acute renal failure caused by drugs and toxins are usually tubulointerstitial where as alcoholic cirrhosis has been shown to cause glomerular involvement.

HEPATORENAL SYNDROME:

Hepatorenal syndrome is defined as acute or subacute functional renal failure occurring in patients with advanced liver failure or portal hypertension[17,18].

The estimated yearly incidence of hepatorenal syndrome in cirrhotics with ascites is about 08% The probability of developing HRS is 18% in one year and 39% at five years[19]. Most of these patients are in advanced stages of decompensated liver disease.

The decrease in effective arterial blood volume and sustained excessive renal vaso constriction , abnormal auto regulation which occurs in advanced stages of cirrhosis along with increasing severity of portal hypertension and abnormal cardiac function together play a role in the development of hepatorenal syndrome in these patients.

Various compounds have been implicated in the pathogenesis of development of hepatorenal syndrome. These include adenosine, natriuretic peptides , nitric oxide, endothelins and endotoxins.

In decompensated liver disease , the increased production of adenosine due to tissue hypoxia triggers a hepatorenal reflex that further leads to a decrease in renal blood flow due to activation of sympathetic nervous system.

ANP and BNP though postulated to have a protective effect by suppressing the stimulation of renin, are raised in patients with decompensated chronic liver disease thus showing the presence of increased resistance to atrial natriuretic peptide in these patients. Nitric oxide plays an important role in causing renal injury in cirrhotics. It controls the arteriolar tone and causes splanchnic vasodilation and also reduces renal blood flow resulting in progressive renal injury.

Endothelins are powerful vasoconstrictors implicated in the pathogenesis of hepatorenal syndrome. They are produced in increased amounts in cirrhotics . Intrarenal imbalance between the vasoconstrictors and vasodilators like prostaglandins affects the renal arterial blood flow contributing to renal injury.

Endotoxins are produced from the colonization of the patient's gut with bacteria and they act as systemic vasodilators. Since they are not degraded by the reticuloendothelial system due to diminished immune competence seen in these patients they are present in considerable amounts to cause splanchnic and systemic arterial vasodilation thus affecting the renal blood flow.

The renal autoregulation curve is shifted to the right in cirrhotic patients making them more vulnerable to the development of renal failure[20].

Increased portal pressure is associated with decreased renal blood flow due to increased sympathetic activity to the renal vessels. This Hepato renal reflex contributes to renal failure in cirrhotics.

The presence of systemic arterial vasodilatation in advanced cirrhosis leads to a hyperdynamic circulation with increased heart rate, high cardiac output and reduced peripheral vascular resistance . In addition there is a new concept termed as cirrhotic cardiomyopathy consisting of myocardial thickening, diastolic dysfunction at rest, and systolic dysfunction under conditions of stress.

Because of these factors the heart is unable to further increase its cardiac output in periods of stress like sepsis, resulting in further compromise of renal circulation and predisposition to the development of hepatorenal syndrome.[21-24].

Hepatorenal syndrome is a diagnosis of exclusion. The criteria for diagnosis of heptorenal syndrome include major and minor criteria.

MAJOR CRITERIA :

1. Acute or Chronic liver disease with advanced hepatic failure and portal hypertension
2. Serum creatinine >1.5 mg/dl or CrCl <40 ml/min
3. Absence of treatment with nephrotoxic drugs, shock, infection or gastrointestinal fluid losses
4. No sustained improvement in renal function after diuretic withdrawal and volume expansion with 1gm/kg of albumin upto a maximum of 100 grams.
5. Proteinuria < 500 mg/dl and no ultrasonographic evidence of parenchymal renal disease.

MINOR CRITERIA:

1. Urine volume < 500 ml/day
2. Urine sodium <10 mEq/L
3. Urine osmolality more than plasma osmolality
4. Urine red blood cells < 50 per high power field
5. Serum sodium concentration <130 mEq/L

All the major criteria are essential where as minor criteria are supportive but not essential for diagnosis of Hepatorenal syndrome.

The classification of Hepato renal syndrome [25] proposed by INTERNATIONAL ASCITES CLUB is as follows:

Type 1: Cirrhosis with rapidly progressive acute renal failure.

Type 2: Cirrhosis with subacute renal failure

Type 3: Cirrhosis with Type 1 or Type 2 HRS superimposed on chronic kidney disease .

Type 4: Fulminant liver failure with Hepatorenal syndrome

Patients present with increased serum creatinine ,reduced creatinine clearance and low urine output.

TYPE 1 HEPATORENAL SYNDROME:

Type 1 HRS is characterized by a rapidly progressive renal failure , defined as doubling of the initial serum creatinine to a level >2.5 mg/dl in less than two weeks. It usually develops following a precipitating event but can occur spontaneously. Patients are usually very ill , with severe jaundice ,coagulopathy and liver failure.

Cardiac and adrenal dysfunction further exacerbate the circulatory dysfunction in type 1 HRS. Tachycardia is less prominent in patients with HRS. Adrenal dysfunction is important in contributing to hemodynamic disturbances in relating to type 1 HRS related to sepsis.

Excessive use of diuretics, repeated abdominal paracentesis without intravascular volume replacement in patients with refractory ascites and blood loss from gastrointestinal tract are well known precipitants of type 1 HRS.

Other triggers are conditions that worsen the arterial vasodilation like sepsis [26] especially spontaneous bacterial peritonitis or surgical jaundice , as the bile acids act as vasodilators. If left untreated the median survival of type 1 hepatorenal syndrome is two weeks[27]

Type 2 HRS:

It is characterized by moderate renal failure with serum creatinine between 1.5 to 2.5 mg/dl. It usually evolves over weeks to months , typically in patients with ascites refractory to diuretic therapy.

Type 2 HRS is felt to be an extension of refractory ascites when hemodynamic changes worsen over time. Patients with type 2 HRS are usually less critical compared with those with type 1 HRS with a milder degree jaundice and coagulopathy.

Precipitating factors are usually absent in type 2 HRS . But many patients with type 2 HRS progress to the more severe type 1, often because of a precipitating event.

If left untreated the mortality of type 2 HRS is 50% at six months.

Type 3 HRS:

Cirrhotics with co existent renal disease are more prone to develop hepato renal syndrome. Several studies have shown that cirrhotics developing hepatorenal syndrome already have a co existing kidney disease[28,29]. The pre existing renal disease may be hypertensive or diabetic nephropathy or chronic glomerulonephritis. The acute renal injury may be in the form of acute tubular necrosis or others. These patients are subjects for combined liver kidney transplant and further studies are needed to validate this strategy.

Type 4 HRS:

Patients with acute liver failure sometimes develop refractory ascites and extremely high portal pressure which predisposes them to HRS. But the data about type 3 and type 4 HRS has not been validated.

The work up should consist of a full septic work up, including blood cultures , chest x ray ,urine and sputum cultures, a diagnostic paracentesis to exclude spontaneous bacterial peritonitis and swabbing any possible source of infection.

An urinalysis to assess for casts, proteinuria and hematuria should be done to exclude organic kidney disease. An abdominal ultrasound should be done to exclude contracted kidneys or other structural

abnormalities of kidneys or post renal failure resulting from obstruction to passage of urine like bladder neck obstruction.

A trial of diuretic withdrawal , together with intravascular volume replacement can replenish the effective arterial blood volume. The intravascular volume replacement is albumin at a dose of 1 gram per kilogram body weight upto a maximum of 100 grams per day.

TREATMENT OF HEPATORENAL SYNDROME:

The rationale for various treatment options for hepatorenal syndrome include improving the effective arterial blood volume through volume expanders and reducing the extent of splanchnic and systemic arterial vasodilation through vasoconstrictors. Portal hypertension can be treated with transjugular intrahepatic porto systemic shunt. MARS is one of the treatment options for elimination of toxins which act as vasodilators. Treatment of liver dysfunction and elimination of portal hypertension is through liver transplantation.

The precipitating source of HRS must be removed in the form of treatment of infection, withdrawal of nephrotoxic medications, including diuretics and nonsteroidal anti inflammatories.

Also antihypertensive agents like ACE inhibitors and angiotensin II antagonists should be stopped because in patients with decompensated cirrhosis RAAS is vital to the maintenance of arterial pressure and GFR in the face of marked peripheral vasodilatation. Inhibition of RAAS may precipitate hypotension and deterioration of renal function.

Albumin improves the effective arterial blood volume .The recommended dose is 20 to 40 grams of albumin in combination with vasoconstrictors, after the initial dose of one gram per kilogram body weight on the first day. Albumin alone appears to be ineffective in the treatment of HRS[30,31]

The peritoneovenous shunt drains ascitic fluid into the internal jugular vein, thus achieving sustained central volume expansion. It has failed to demonstrate any survival advantage in HRS and therefore is no longer used because of significant complications such as coagulopathy, postoperative sepsis and shunt occlusion [32,33]. Also PV shunts are no longer in production leading to inexpertise in inserting PV shunts.

Renal vasodilators like low dose dopamine, prostaglandin E1 analogues like misoprostol or endothelin receptor antagonists have no proven efficacy in the treatment of type 1 Hepatorenal syndrome [34].

Systemic vasoconstrictors by reducing the extent of systemic vasodilation, lead to a rise in the systemic arterial blood pressure, which in turn increases the renal perfusion pressure.

Midodrine is an alpha agonist which raises systemic vascular resistance and renal perfusion pressure. A mean arterial pressure of > 70 mm Hg should be maintained.

Octreotide is a synthetic analogue of somatostatin which decreases splanchnic circulation which is given by intravenous infusion or subcutaneously.

Vasopressin is a V1 receptor agonist which causes vasoconstriction of systemic and splanchnic circulation . But it is not commonly used because of ischemic side effects.

Terlipressin is a vasopressin analogue with less ischemic side effects and improves renal function better than vasopressin.

Norepinephrine is an alpha and beta adrenergic agonist which causes systemic vasoconstriction. It has no significant ischemic side effects.

Isolated case reports have suggested the useof N-acetylcysteine (NAC) in combination with systemic vasoconstrictors or endothelin receptor antagonists. This is based on a small case study of twelve patients with HRS who showed an improvement in serum creatinine

after an intravenous infusion of NAC, but it is not standard clinical practice at this time[35,36].

Transjugular intrahepatic shunt is a prosthesis that bridges an intrahepatic branch of portal vein with the hepatic radicle. It is effective in reducing portal pressure. It also returns a significant part of the splanchnic vascular volume into the systemic circulation .

To date , there are no controlled studies assessing the efficacy of TIPS for the management of HRS. An improvement in renal function has been observed , but this improvement falls short of normalization of the GFR. However , in one study where vasoconstrictor therapy was followed by TIPS insertion, TIPS was able to normalize renal function over the course of 12 months. The overall survival was 50% [37,38].

Albumin dialysis removes albumin- bound substances, such as cytokines and bile acids , which are also systemic vasodilators. Albumin dialysis can filter out creatinine and artificially reduces the serum creatinine without changing the GFR. It can create a false sense of improvement when there is no recovery of renal function. But there is not enough data to accept it as standard of care.

Liver transplantation corrects liver dysfunction and eliminates portal hypertension . Renal function improves in many patients after transplantation, but up to 40% of patients can remain dependent on dialysis.

Liver transplantation is the treatment of choice for type 1 and type 2 HRS.[39]. Intermittent hemodialysis has been used as a short term bridge to liver transplantation. However ,there is no evidence that it increases long term survival without transplantation.

PREVENTION OF HEPATO RENAL SYNDROME:

One third of patients with patients with spontaneous bacterial peritonitis will develop renal impairment despite appropriate antibiotic therapy. Patients who receive albumin in addition to antibiotics have been shown to have a lower incidence of renal impairment and death compared to those treated with antibiotics alone. Patients in this study received intravenous albumin at a dose of 1.5 gram per kilogram bodyweight on day 1, then one gram per kilogram body weight on day 3[40]. Although antibiotics alone have not been shown to directly reduce the incidence of HRS , primary prophylaxis of spontaneous bacterial peritonitis with norfloxacin reduces the incidence of SBP by 28% which itself is a risk factor for HRS.

Removal of large volume (>5 liters) of fluid may precipitate circulatory dysfunction , which can induce renal failure in up to 20 % of patients. Giving albumin at a dose of eight grams per litre of ascetic fluid removed has been shown to reduce the incidence of renal failure but not mortality.[41]

There is no specific measure adopted for the prevention of type 2 HRS because patients usually have no precipitating factors for developing this variant of HRS. Treatment of refractory ascites and hyponatremia is highly useful in preventing the occurrence of type 2 hepato renal syndrome.

Pentoxyphylline is a non selective phosphodiesterase inhibitor which has been tried in patients with alcoholic hepatitis. In one study, its use was associated with 40% reduction in mortality, thought to be secondary due to a 65% reduction in the occurrence of hepatorenal syndrome. Patients in this study were quite ill , with jaundice and Maddrey discriminant factor more than or equal to 32.

EVALUATION OF RENAL FAILURE IN PATIENTS WITH CIRRHOSIS:

Patients with cirrhosis who are at risk for renal injury should undergo regular evaluation to detect renal dysfunction at the earliest because it is an important risk factor impacting the survival the of these patients before and after liver transplantation and there is a significant improvement in morbidity and mortality who undergo liver transplantation earlier based on their MELD scoring which takes into account their status of renal reserve.

Apart from conventional bio markers like blood urea, serum creatinine, urinalysis for deposits and casts various other tests should be performed to find out if it is prerenal failure or the more severe hepatorenal syndrome because prerenal failure improves with intravascular volume expansion where as hepatorenal syndrome is difficult to treat.

The tests include

1.Serum creatinine :

This is to be measured everyday in patients with acute renal dysfunction . An increase in serum values by 0.3 to 0.5 mg/dl indicates severe reduction in glomerular filtration rate.

2. Serum electrolytes:

Serum sodium and Potassium should be measured frequently in these patients. Dilutional hyponatremia is common in these patients and the presence of hyperkalemia necessitates the withdrawal of potassium sparing diuretics.

3.Urinalysis:

24 hour urine samples should be examined in these patients for urinary sediment abnormalities and presence of significant proteinuria favours the presence of intrinsic renal failure rather than functional renal failure.

4) Ultrasound Abdomen:

Urinary tract obstruction should be ruled out which can cause post renal failure. Presence of contracted kidneys indicates the presence of chronic kidney disease . Presenc of normal kidneys is suggestive of functional renal failure.

5) Renal biopsy:

Renal biopsy can be tried when intrinsic renal failure is suspected and the cause of it could not be identified. It also helps in making a decision about the need for combined liver and kidney transplantation such as in patients with coexisting renal dysfunction. But renal biopsy is

contraindicated if the patient has got coagulation abnormalities or active bleeding.

EVALUATION OF LIVER FUNCTION:

Apart from liver function tests and abdominal ultrasonogram , a liver biopsy can be performed if the cause of liver cirrhosis could not be identified and there are no active bleeding or coagulation abnormalities.

ASSESSMENT FOR BACTERIAL INFECTION :

A high degree of suspicion is necessary to identify bacterial infection because these patients may not have an elevated leukocyte count due to hypersplenism . Cirrhotics with ascites must have a diagnostic paracentesis for ascitic cell count and culture.

A chest x-ray must be taken to rule out any respiratory focus of infection. Blood and Urine cultures must be done .

ASSESSMENT OF RENAL FUNCTION:

To date plasma creatinine is the most commonly used method to evaluate the status of renal function. But it is highly inaccurate and

inferior compared to the measurement of glomerular filtration rate. Glomerular filtration rate is defined as the amount of plasma that is filtered through glomeruli per unit time.

Normal GFR varies according to age, sex and body size. In young adults it is approximately 120-130 ml/min/m^2 and it declines with age.

The gold standard procedure for measurement of GFR is urinary clearance of an ideal filtration marker. An ideal filtration marker is one that is freely filtered at the glomerulus , present at a stable plasma concentration and one that is not reabsorbed ,secreted or metabolized by the kidney.

The ideal filtration marker is inulin. However this is rarely used and alternative markers like iohexol and iothalamate are more commonly used. Apart from being expensive , it also poses high risk for patients and difficult to perform in resource limited settings.

Creatinine is generated from the precursor creatine in muscle. It has a molecular weight of 113 k DA and is mainly eliminated by kidneys through glomerular filtration. There is some amount of tubular secretion.

The assays employed for estimation of creatinine varies in different laboratories leading to significant variation in their levels.

As a result of variation in these processes especially creatinine generation, the cut off for normal versus abnormal serum creatinine concentration differs among groups.

Serum creatinine is an insensitive marker as the GFR is usually reduced by 50% before serum creatinine starts raising above the upper reference range. So far creatinine has been considered the renal marker of choice because it is a naturally occurring endogenous compound that is freely filtered at the glomerulus and has relatively minor absorption and secretion by the renal tubules. Though serum creatinine determination remains the most commonly used renal marker for estimation of glomerular filtration rate, it is known to have a number of inherent difficulties which affects its clinical reliability.

FACTORS AFFECTING SERUM CREATININE CONCENTRATION:

1) Older age :

Serum creatinine decreases due to reduced creatinine generation from age related decrease in muscle mass.

2) Sex :

Female gender have reduced serum creatinine because of reduced muscle mass.

3) Race:

Serum creatinine increases due to higher race creatinine generation as a result of higher average muscle mass in African Americans compared to Caucasians.

4) Diet:

Vegetarian diet causes a decrease in creatinine generation where as ingestion of cooked meat causes transient increase in creatinine generation, however this may by blunted by transient increase in GFR.

5) Body habitus:

A) A muscular person has an increase in serum creatinine as a result of increased muscle mass and increased protein intake.

B) Malnourished /Amputated person has a decrease in serum creatinine from reduced muscle mass and decreased protein intake.

C) An obese person does not have a significant change in creatinine values as the excess mass is fat which does not contribute to creatinine generation.

GFR can be measured by timed urinary collection for creatinine. Creatinine clearance is usually determined by using venous blood for serum creatinine and a 24 hour urine sample. For a substance that is cleared by urinary excretion the clearance formula is

$$Cx = Ux \times Vx/Px$$

where Ux is the urinary concentration of x and V is the urine flow rate. The term Ux X Vx represents the urinary excretion rate of x.If substance x is freely filtered at the glomerulus ,then urinary excretion represents the net effects of glomerular filtration , tubular reabsorption and secretion.

Because the renal tubules secrete creatinine, measurements of creatinine clearance significantly overestimates the GFR . Accurate measurements of creatinine clearance also requires complete and carefully timed urine collections.

Inadequate urine collections yield spurious results. Repeated measurements of creatinine clearance may overcome some of the errors.

Since the conventional methods used for assessing renal function are more prone to errors newer biomarkers have been evaluated as markers of acute kidney injury . They include

1) Neutrophil gelatinase associated lipocalin:

A 25 k Da protein belonging to lipocalin superfamily , NGAL is one of the earliest markers of ischemic or nephrotoxic injury and is raised in the blood and urine of humans soon after AKI.

In a recent study , it was shown to have a sensitivity and specificity of 90% and 99% respectively for identifying AKI.

2) Kidney injury molecule-1 :

A transmembrane protein, expressed in the renal proximal tubular cells. After an acute insult like ischemia or injury due to use of nephrotoxic drugs their levels are markedly elevated in urine.

Urinary KIM-1 seems to be highly specific for ischemic AKI . In one study it was demonstrated to be helpful in differentiating

ischemic acute kidney injury from prerenal AKI .It is also a predictor of renal replacement therapy and mortality in AKI.

3) N-acetyl -beta(D) glucosaminidase:

A lysosomal brush border enzyme expressed predominantly in the proximal tubular cells, N-acetyl-beta (D) glucosaminidase is a marker of kidney injury indicating renal tubular damage.

4) Interleukin-18:

A proinflammatory cytokine detected in the urine after acute ischemic proximal tubular damage , IL-18 displays good sensitivity and specificity for ischemic AKI with increase in levels prior to serum creatinine by two days.

5) Cystatin –C:

Several studies have been undertaken so far evaluating the use of serum cystatin c and cystatin based formulas for detecting acute renal dysfunction in patients with decompensated chronic liver disease.

It is a cysteine protease inhibitor with a molecular weight of 13 k DA which is synthesised in all nucleated cells. Due to its small size it is freely filtered at the glomerulus, and not secreted but completely reabsorbed by the renal tubules and undergoes catabolism there. So the serum levels of cystatin C are dependent on glomerular filtration as there

is no significant tubular secretion , thus making it a reliable marker of estimating glomerular filtration rate.

The advantage of cystatin C lies in the fact that it is virtually unaffected by age (above one year) , muscle mass, gender and race. Cystatin based formulas are relatively simpler when compared to creatinine based MDRD formulas.

Several cystatin based formulas proposed for the estimation of GFR include Hoek' s formula. Larsson and Grubb formula has been proven to be equally reliable in estimating GFR. The major advantage in using cystatin as a biomarker of renal injury is that it can detect even small changes in GFR and there are no GFR blind areas with cystatin C.

Thyroid status of the patient should be determined before estimating cystatin C levels as it affects their concentration in plasma . Treatment with corticosteroids in patients with decreased renal function has been shown to affect serum cystatin C levels.

DIFFERENTIAL DIAGNOSIS OF ACUTE RENAL FAILURE IN LIVER DISEASE:

It is essential to identify the nature of renal failure in cirrhosis because each type has different line of management.

Parameters	Prerenal failure	Intrinsic renal failure	HRS
History	Excessive fluid loss	Prolonged and sustained volume loss	Decompensated and advanced stage liver failure.
Clinical	Volume contraction	Infection, use of nephrotoxic agent or diuretics	Refractory and tense ascites
Response to fluid challenge	Present	Absent	Absent
Urine sodium	<10	>30	<10
Urinary/plasma creatinine	>30:1	<20 :1	>30 :1
Urinary/ plasma osmolarity	Urine osm>plasma osm	Urine osm= plasma osm	Urine osm> plasma osm
Urine sediments	Absent	Granular cast with cellular debris	Usually absent
Ultrasonogram	High resistive index	High resistive index	High resistive index

History of volume loss followed by onset of renal failure which gets corrected with volume replacement favours pre renal azotemia where as it is not corrected it if it has progressed to acute tubular necrosis.

Hepatorenal syndrome may or may not have precipitating factors and usually responds to volume expansion with intravenous albumin. In urinanalysis presence of hyaline casts is normal and can occur in pre renal azotemia or hepatorenal syndrome where as the presence of renal tubular epithelial cells favours the diagnosis of acute tubular necrosis. Urine sodium, fractional excretion of sodium, urine plasma osmolality ratio, urine and plasma creatinine ratio are not as useful as examination for urinary sediments in differentiating the three most important causes of renal failure in patients with chronic liver disease.

The use of Duplex Doppler Ultrasonogram for the assessment of intra renal hemodynamics , and renal arterial resistive index has been shown to have a significant correlation to plasma renin activity and can be tried in patients with compensated cirrhosis and ascites.[44].

MANAGEMENT OF RENAL FAILURE IN CHRONIC LIVER DISEASE:

General measures:

Cirrhotic patients with acute onset renal dysfunction should be treated aggressively as early interventions can significantly lower the mortality. Precipitating factors like sepsis and blood loss from variceal bleeding due to portal hypertension should be identified and taken care of at the earliest. Third generation cephalosporins are the preferred drugs for the treatment of sepsis in patients with cirrhosis with ascites.

Patients with type 1 hepatorenal syndrome are more prone for developing adrenal insufficiency and treatment with corticosteroids have been shown to be marginally beneficial in these patients.

Administration of excessive fluids should be discouraged as there is increased risk of dilutional hyponatremia and fluid accumulation can lead to massive ascites and respiratory distress in these patients.

After the onset of renal failure, the use of potassium sparing diuretics should be discouraged as there is a possibility of developing hyperkalemia which can lead to cardiac conduction abnormalities and sudden cardiac arrest. Loop diuretics may not be effective in this situation.

Patients with intractable and refractory ascites should be treated with repeated abdominal paracentesis along with adequate intravascular volume replacement like intravenous albumin at a dose of eight grams per liter of fluid removed.

Diuretics should be discontinued if the renal dysfunction is due to overuse of these drugs and isotonic saline can be given if there is hyponatremia along with volume contraction in the absence of extravascular fluid accumulation.

The treatment of hepatorenal syndrome is improving the effective arterial volume through volume expanders , reducing the extent of splanchnic vasodilation through vasoconstrictors and elimination of portal hypertension through transjugular intrahepatic portosystemic shunt and elimination of toxins produced by sepsis which causes circulatory dysfunction.

Hemodialysis and CVVH have been tried as a treatment option for patients with hepatorenal syndrome who are candidates for liver transplantation as a bridge therapy. But there has been no studies which has validated their advantage over pharmacological therapy like vasoconstrictor administration.

Also the procedure is can be complicated by severe bleeding episodes which can lead to hypotension and infection. So it is better to reserve this treatment to those who have no satisfactory response to vasoconstrictor therapy and also in those who develop severe life threatening hyperkalemia and refractory fluid accumulation which results in respiratory distress.

PROGNOSIS OF RENAL FAILURE IN CHRONIC LIVER DISEASE:

Renal failure in a patient with liver disease has got a dismal prognosis. It depends on the type of renal failure. Pre renal azotemia has got a better prognosis where as those with hepatorenal syndrome have got the worst prognosis. Without liver transplantation the mortality rate is 50% at one month and 80% at six months.

The use of vasoconstrictor therapy does not improve the mortality rate in these patients with hepatorenal syndrome but if they respond to vasoconstrictor therapy they have a significant level of better prognosis than those non responders[43] .

PREVENTION OF RENAL FAILURE IN CIRRHOSIS:

The patients with cirrhosis at risk of developing bacterial infections include

1) Child pugh score >10
2) Ascitic fluid protein content < 1.5 grams/dl
3) Plasma sodium level < 130 mmol/L
4) Serum bilirubin > 3 mg/dl .

In these patients prophylaxis with oral norfloxacin 400 mg/day has been shown to reduce the incidence of spontaneous bacterial peritonitis . The proposed mechanism for this is the inhibition of translocation of microbial organisms from the gut to the peritoneum.

Also albumin given on the day of admission and on day three intravenously has been shown to reduce the incidence of spontaneous bacterial peritonitis and hepatorenal syndrome.

Avoiding diuretic abuse and judicious use of aminoglycosides will go a long way in preventing the development of iatrogenic renal failure.

RENAL FAILURE AND LIVER TRANSPLANTATION:

Patients at risk of renal failure are suitable candidates for liver transplantation . Pre treatment with vasopressors and albumin has been shown to improve the outcome after transplantation.

Studies have shown that in cirrhotics who have refractory ascites but not yet developed hepatorenal syndrome, liver transplantation has been shown to have a dramatic improvement in renal function and this shows that liver transplantation should be done as early as possible in cirrhotics who are suitable candidates for liver transplantation.

COMBINED LIVER KIDNEY TRANSPLANTATION:

The exact factors determining the need for combined liver and kidney transplantation have not been identified as yet. Presence of hepatorenal syndrome alone does not necessarily need combined liver transplantation because only liver transplantation has been shown to reverse the renal dysfunction in these patients. But the duration for which the patient has undergone renal replacement therapy before undergoing liver transplantation is a relatively reliable indicator for determining the presence of irreversible renal failure which necessitates combined liver kidney transplantation.

Studies have shown that patients who have undergone renal replacement for atleast three months before undergoing transplantation have an improved survival with combined liver kidney transplantation.

MATERIALS AND METHODS

INCLUSION CRITERIA:

After they gave informed consent, 50 patients undergoing treatment for chronic liver disease as in- patients in the Department of General Medicine, Tirunelveli Government Medical College,Tirunelveli participated in the study.

The criteria for chronic liver disease is defined by

1. Compatible clinical profile (History, Ascites with or without jaundice)
2. Ultrasound evidence (reduced liver span/altered echo texture of liver)
3. Biochemical profile (abnormal liver function tests or reversal of albumin- globulin ratio)

EXCLUSION CRITERIA:

- Age > 60 years
- Known primary renal disease
- Refractory ascites
- Severe encephalopathy
- History of recent gastrointestinal bleed
- Thyroid dysfunction
- Diabetes mellitus
- Hypertension
- Patients receiving corticosteroid therapy, Angiotensin converting enzyme inhibitors.

METHODOLOGY

This analytical study was conducted in 50 eligible patients admitted for chronic liver disease with apparently normal renal function in the medical wards in our hospital from August 2011 to August 2012.

All patients underwent a thorough clinical examination, including medical history.

Urinalysis including 24 hours urine volume and urine creatinine were done after stopping diuretics for three days and biochemical profile including liver function tests, viral markers for hepatitis B, renal function tests were done and results were noted .

After assessing thyroid status of the patient ,serum cystatin was estimated with the same sample used for evaluation of plasma creatinine. Data about demographic variables, clinical features were collected using a proforma.

Ultrasound Abdomen was done in all the patients to assess liver size and echotexture , presence of splenomegaly, portal vein dilatation, presence of collaterals around spleen, presence of ascites and structural renal abnormalities.

Estimated Creatinine clearance was calculated using Cockcroft- Gault formula(CGF)

$$\frac{(140\text{-Age}) \times \text{Body weight in kilogram}}{\text{Serum Creatinine} \times 72.}$$

If the patient is female the above value has to be multiplied by 0.85.

Measured creatinine clearance was calculated by the formula

$$\frac{(\text{Urine creatinine} \times \text{24 hours urine volume})}{\text{serum creatinine.}}$$

This value was divided by 1440 to get the GFR in ml/min

Estimated creatinine clearance using serum Cystatin was calculated using Hoek' s formula , GFR = -4.32 + (80.35 X 1/Cys C). Comparison of GFR obtained by the above methods was done .

STATISTICAL ANALYSIS

The continuous variables of two groups of study subjects were compared between attributes by student independent 't' test. More than two groups of variables were compared between the categories by ANOVA (Analysis of variances) and the significance between the two groups were tested by post coc test of Bonferrani. The category variables were compared by Chi square test. The above statistical procedures were performed by the statistical package IBM SPSS 20. The 'p' value less than 0.05 ($p<0.05$) was considered as significant.

OBSERVATIONS AND ANALYSIS

50 patients with chronic liver disease who fulfilled the inclusion criteria participated in the study.

The observations made are as follows:

AGE:

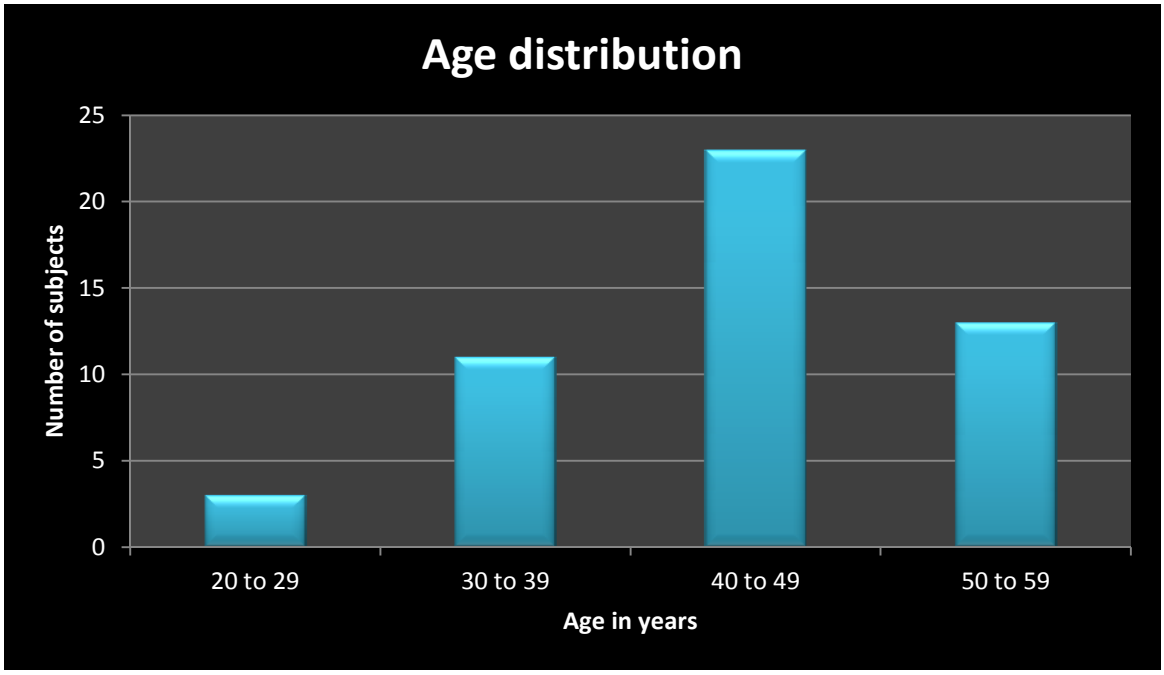
Among the study group the minimum age was 24 years and maximum age was 58 years.

The mean age was 43.5 years.

Table1:

AGE GROUP (YEARS)	NUMBER OF PATIENTS	PERCENTAGE
20-29	03	06%
30-39	11	22%
40-49	23	46%
50-59	13	26%
TOTAL	50	100%

Chart1:



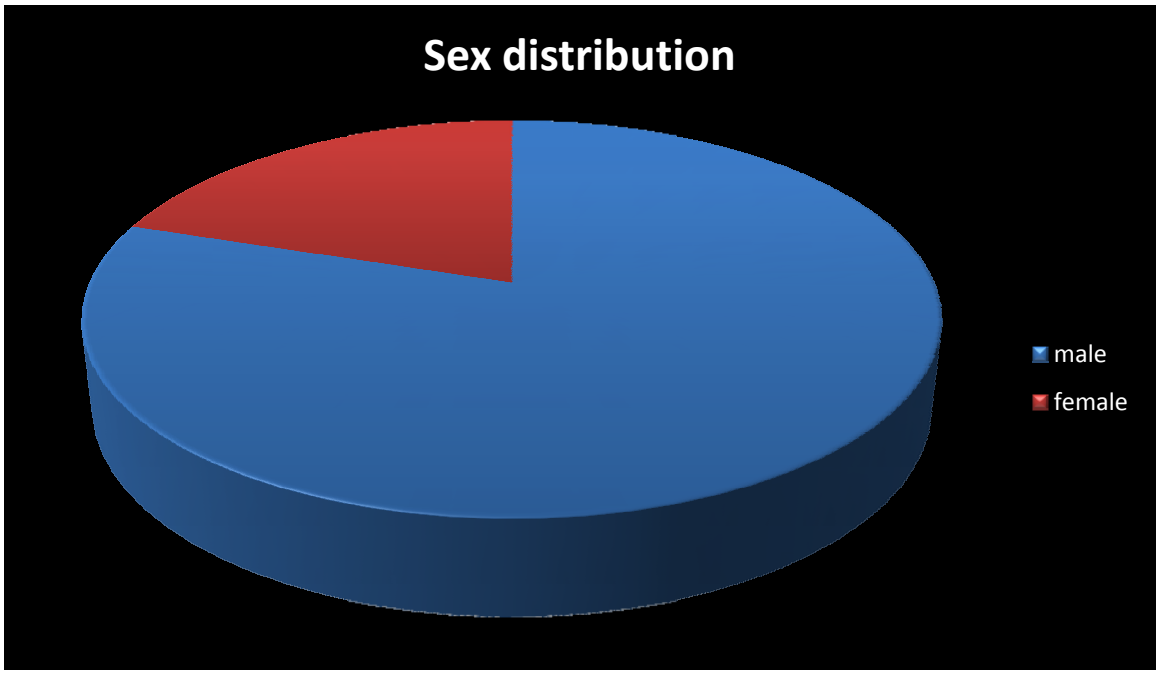
SEX DISTRIBUTION:

Of the 50 patients 40 were male and 10 were female.

Table2:

Age group (Years)	Male (number)	Percentage (%)	Female (number)	Percentage (%)
20 to 29	01	2.5	02	20
30 to 39	08	20	03	30
40 to 49	22	55	01	10
50 to 59	09	22.5	04	40
TOTAL	40	100	10	100

Chart2:

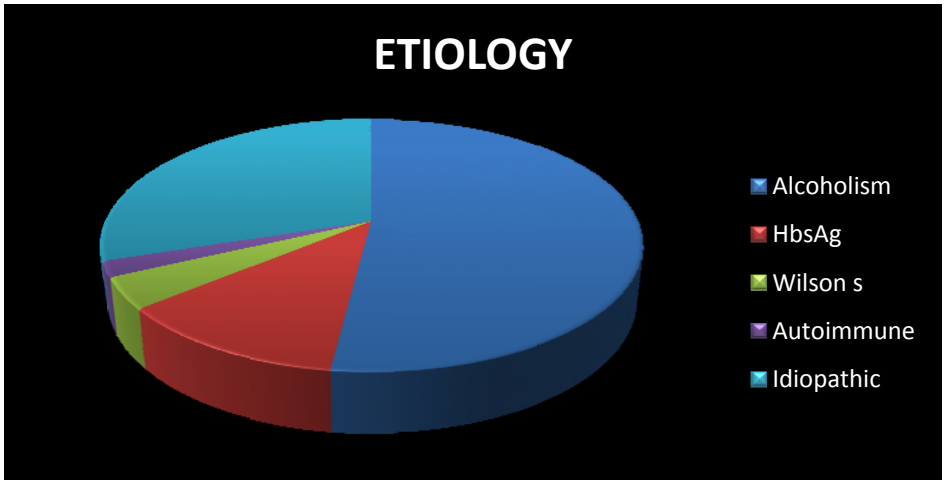


ETIOLOGY OF CHRONIC LIVER DISEASE:

Alcoholism was found to be the major cause of chronic liver disease followed by HbsAg . The other causes were Wilson' s disease and Autoimmune . Causes could not be identified in 15 patients.

Table3:

Causes	Male	Female	Total
Alcohol	26	00	26
HbsAg	02	04	06
Wilson's	01	01	02
Autoimmune	00	01	01
Idiopathic	11	04	15
Total	40	10	50



Alcoholism was found to be the major cause of cirrhosis in males where as HbsAg positivity was found to be a major cause in females .

CLINICAL CHARACTERISTICS OF STUDY PARTICIPANTS:

Study subjects according to their bio- chemical parameters are as follows:

Table4:

Variable	Serum Bilirubin (mg/dl)	Serum Albumin (gm/dl)	PT (Sec)	blood urea(mg/dl)	Serum Creatinine (mg/dl)	Serum. Cystatin (mg/L)	Urine value	Urine Creatinine
Mean	5.0	3.2	14.9	28.0	0.93	1.4	1446.8	59.1
SD	5.7	0.6	3.0	9.3	0.19	0.5	424.7	13.2
Min	1.0	1.8	12.0	15.0	0.6	0.73	400.0	43.0
Max	25.5	4.6	27.7	54.0	1.4	3.10	2300.0	102.0

The mean serum bilirubin was 5 mg/dl , serum albumin was 3.2 mg/dl, mean prothrombin time was 14.9 seconds, serum creatinine was 0.93 mg/dl, mean serum cystatin value was 1.4 mg/L

The blood urea levels were within normal limits and did not rise markedly even in patients with diminished GFR indicating that it is an unreliable marker for assessing renal function .

The mean blood urea level was 28 mg/dl.

COMPARISON OF BIOCHEMICAL CHARACTERISTICS BETWEEN CASES WITH KNOWN CAUSES AND IDIOPATHIC:

The bio- chemical parameters were compared in cases with known cause for chronic liver disease and those with idiopathic cirrhosis.

Table5:

variables	Causes				Difference b/w means	't'	df	Significance.
	Present n=35		Absent n=15					
	Mean	SD	Mean	SD				
Sr.bilirubin	6.0	6.4	2.1	1.1	3.9	2.241	48	P<0.05
Sr. albumin	3.2	0.6	3.1	0.5	0.1	0.429	48	P>0.05
PT (Sec)	15.1	3.3	14.4	2.1	0.7	0.822	48	P>0.05
Blood urea	27.6	9.3	29.1	9.4	1.5	0.516	48	P>0.05
Sr. Creatinine	0.9	0.2	1.0	0.2	0.1	2.524	48	P<0.05
Sr. Cystatin	1.36	0.57	1.44	0.35	0.08	0.444	48	P>0.05
Urine volume of 24 hours	1458.9	448.5	1415.6	370.1	43.5	0.320	48	P>0.05
24hr. U.Creatinine	59.7	15.0	59.6	7.3	2.1	0.516	48	P>0.05

It was found that there was no significant difference in serum albumin, PT (Sec), blood urea, serum cystatin, urine volume of 24 hours and urine creatinine of 24 hours ($P>0.05$). The serum bilirubin of subjects with known causes was 6.0±6.4 and subjects with idiopathic causes was 2.1±1.1 and the difference was statistically significant ($P<0.05$). Similarly the serum creatinine of subjects with known causes was 0.9±0.2 and subjects with idiopathic causes was 1.0±0.2 and the difference was statistically significant ($P<0.05$).

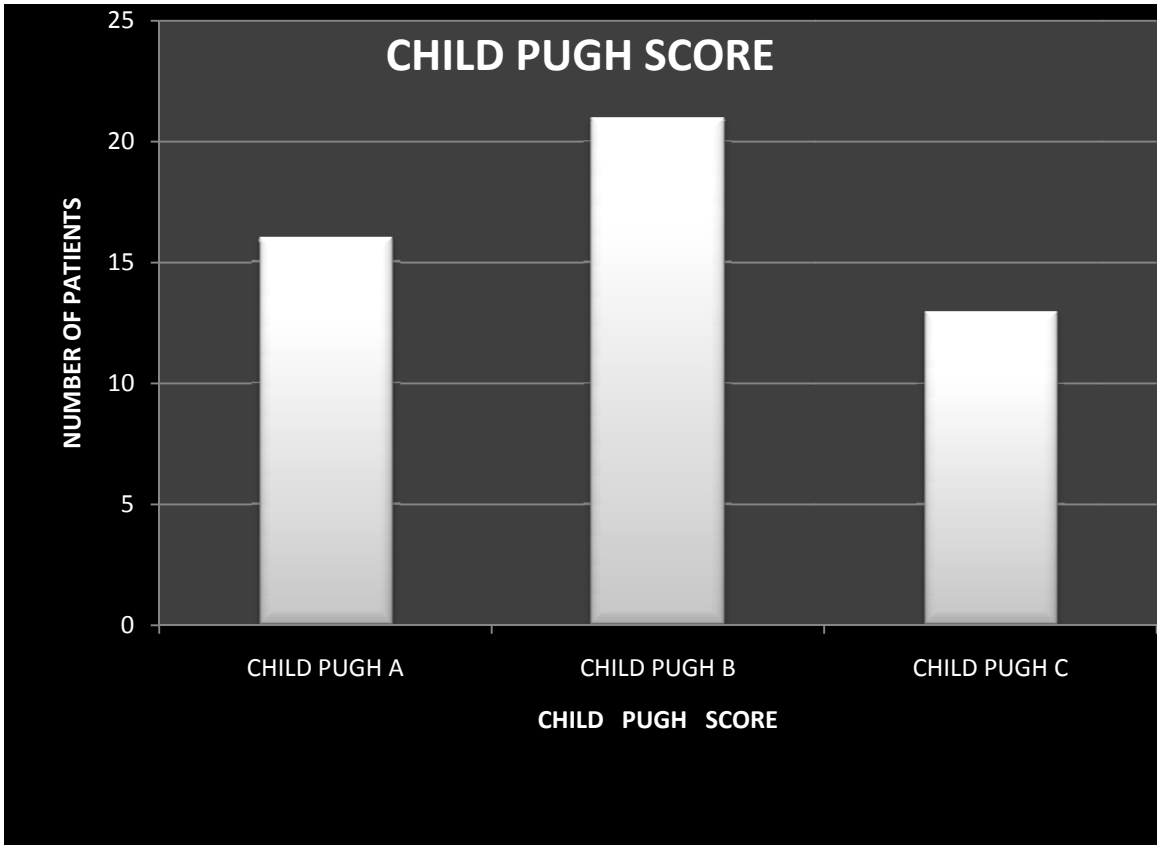
GRADING OF SEVERITY BY CHILD –PUGH SCORE:

Patients with score 5 to 6 fall under Grade A. Grade B includes scores from 7 to 9. Scores above 9 is Grade C. Of the 50 patients, sixteen patients belonged to Grade A, 21 came under Grade B and 13 were in Grade C.

Table6:

	Number of patients	**Percentage**
Child Pugh A	16	32%
Child Pugh B	21	42%
Child Pugh C	13	26%

Chart4:



The mean score in Child Pugh A was 5.9, 8.0 in Child Pugh B and 10.7 in Child Pugh C.

GFR BY COCKCROFT-GAULT METHOD:

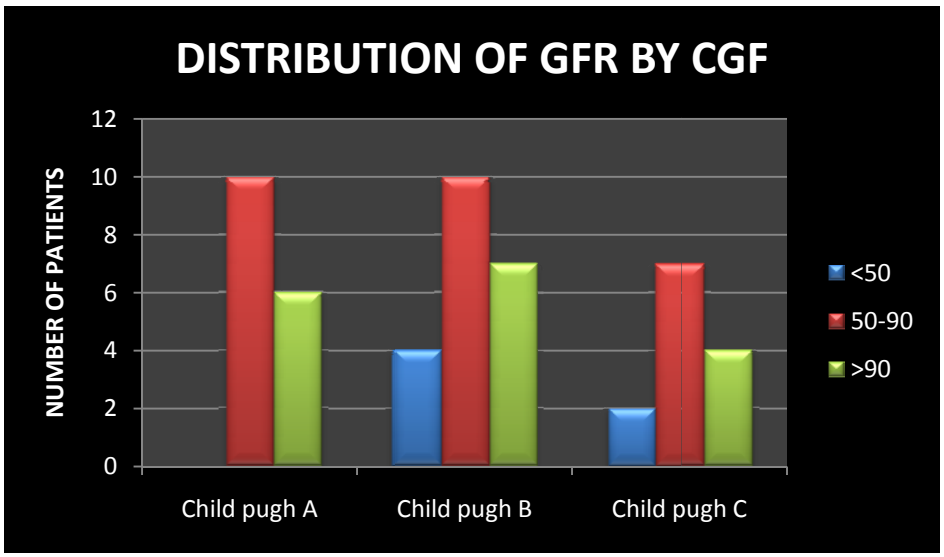
GFR was calculated by Cockcroft- Gault formula and the following were noted.

Table7:

Grading	GFR <50 ml/min	50-90 ml/min	>90 ml/min
Child Pugh A	0	10	06
Child Pugh B	04	10	07
Child Pugh C	02	07	04

According to CGF, none of the patients in Child Pugh A had GFR <50 ml/minute, and only two (15.38%) patients in Child Pugh C had GFR < 50 ml/min.

Chart5:`



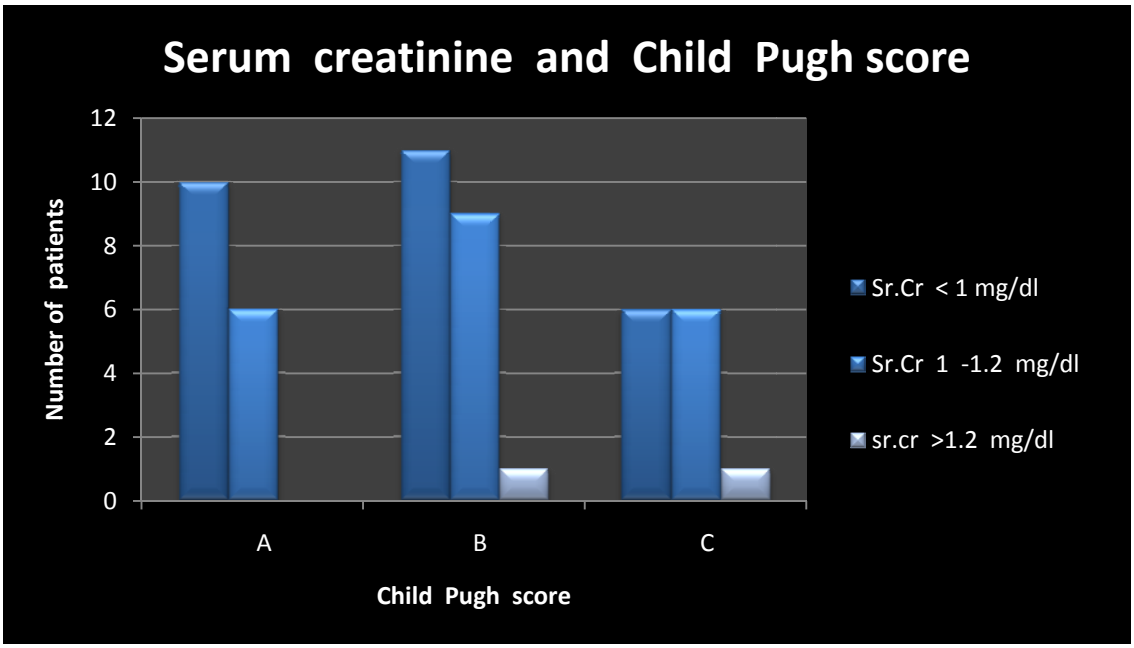
SERUM CREATININE AND CHILD PUGH SCORE:

The levels of serum creatinine across varying grades of Child Pugh scoring is as follows.

Table no 8:

CHILD PUGH SCORE	Serum Creatinine (<1 mg/dl)	Sr.Creatinine (1 -1.2 mg/dl)	Sr.creatinine (>1.2 mg/dl)
A	10	06	0
B	11	09	01
C	06	06	01

Chart no 6



Of the 16 subjects in Child Pugh A group 10 (62.5%) had a serum creatinine value of less than one mg/dl and none of them had creatinine levels above 1.2 mg/dl.

Of the 21 subjects in Child Pugh B , 20 had their serum creatinine levels within normal limits where as only one patient (4.76%) had serum creatinine above 1.2 mg/dl.

Of the 13 subjects with Child Pugh score C, six (46.13%) of them had their creatinine levels less than one and only one patient (7.69%) had his values more than 1.2 mg/dl.

SERUM CYSTATIN C AND CHILD PUGH SCORE:

Serum cystatin C compared across different grades of Child Pugh score is

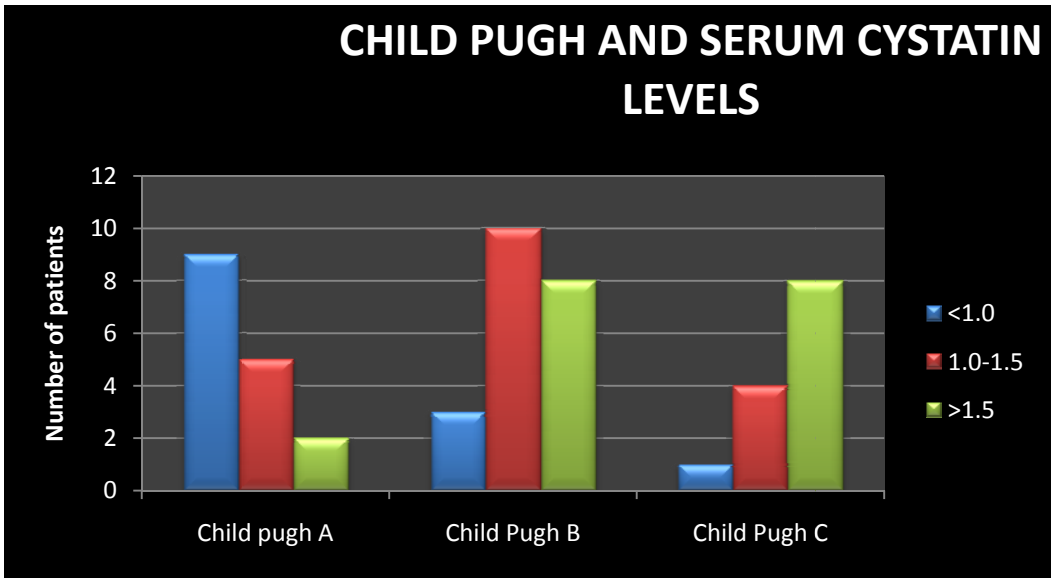


Table no 9:

CHILD PUGH SCORE	S.CYSTATIN (<1mg/L)	S.Cystatin (1-1.5mg/L)	S.Cystatin >1.5(mg/L)
A	9	5	2
B	3	10	08
C	1	04	08

Of 16 patients in Child Pugh A nine patients (56.25%) had serum cystatin levels less than one where as only one patient (7.69%) in Child

Pugh C had cystatin levels less than one. Eight (61.53%) out of thirteen patients had serum cystatin levels more than 1.5 in Child Pugh C . This shows that serum cystatin levels increase as the degree of liver dysfunction increases.

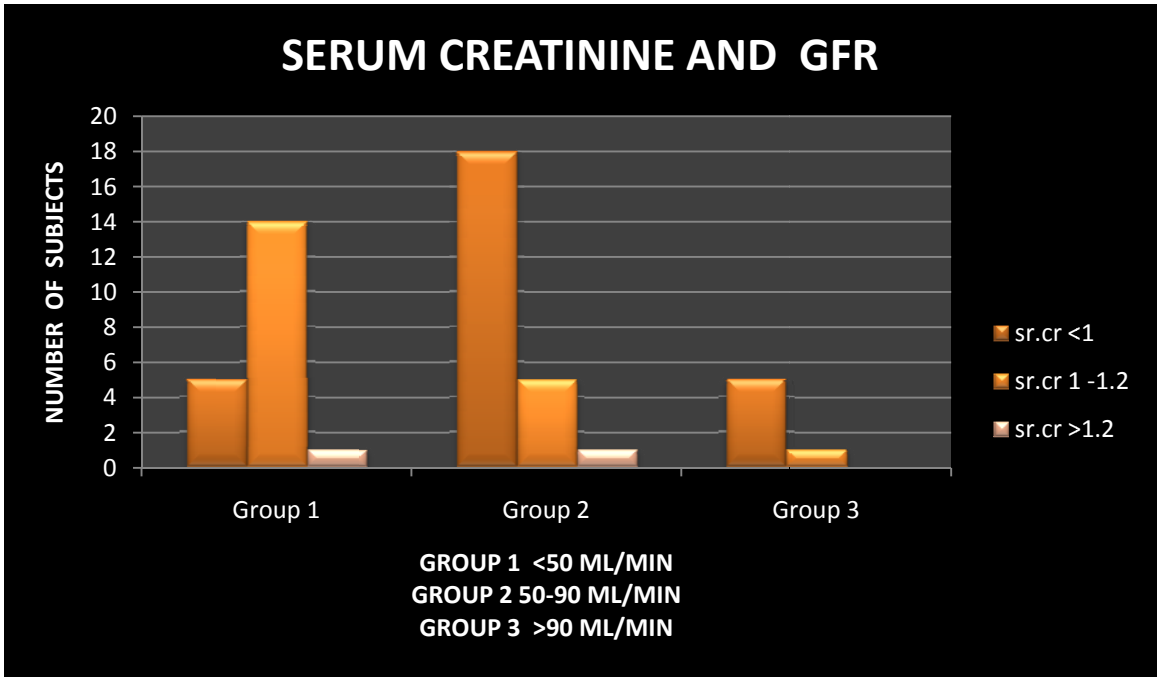
The mean cystatin level in Child Pugh A was 1.05 where as it was 1.47 in Child Pugh B and 1.66 in Child Pugh C.

SERUM CREATININE AND GFR :

Study subjects were classified into three groups based on their GFR calculated based on cystatin C . Group I had a GFR < 50 ml/min. Group II had GFR between 50-90 ml/min where as Group III had GFR above 90 ml/min.

Table no 10:

	S.Cr<1 mg/dl	**S.Cr 1 to 1.2 mg/dl**	**S.Cr >1.2 mg/dl**
Group I	05	14	01
Group II	18	05	01
Group III	05	01	00



Of the 20 patients with GFR below 50 ml/min ,19 (95%) had serum creatinine values below 1.2 mg/dl and only one patient (5%) had serum creatinine values above 1.2 mg/dl indicating that even though patients have a reduced GFR the serum creatinine levels fail to raise above the normal limits correspondingly.

CHILD PUGH AND GFR ESTIMATED BY CYSTATIN C:

Hoek's formula is a cystatin C based formula for estimating GFR. The GFR across varying grades of GFR is as follows.

Chart no 9:

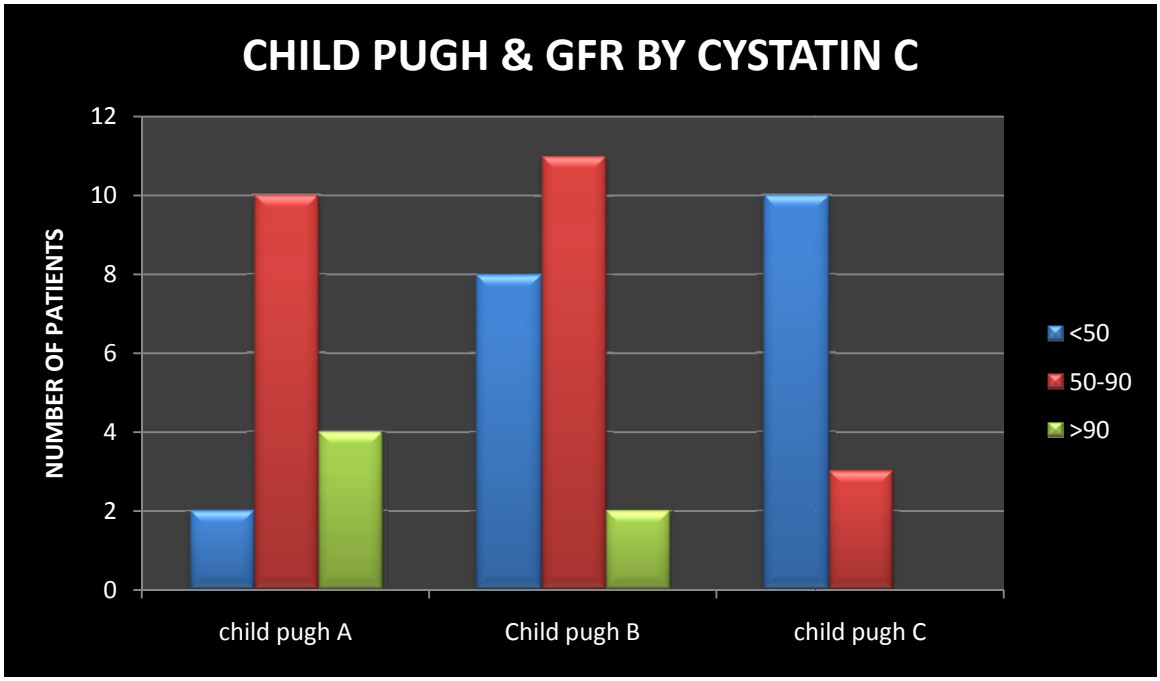


Table no 11:

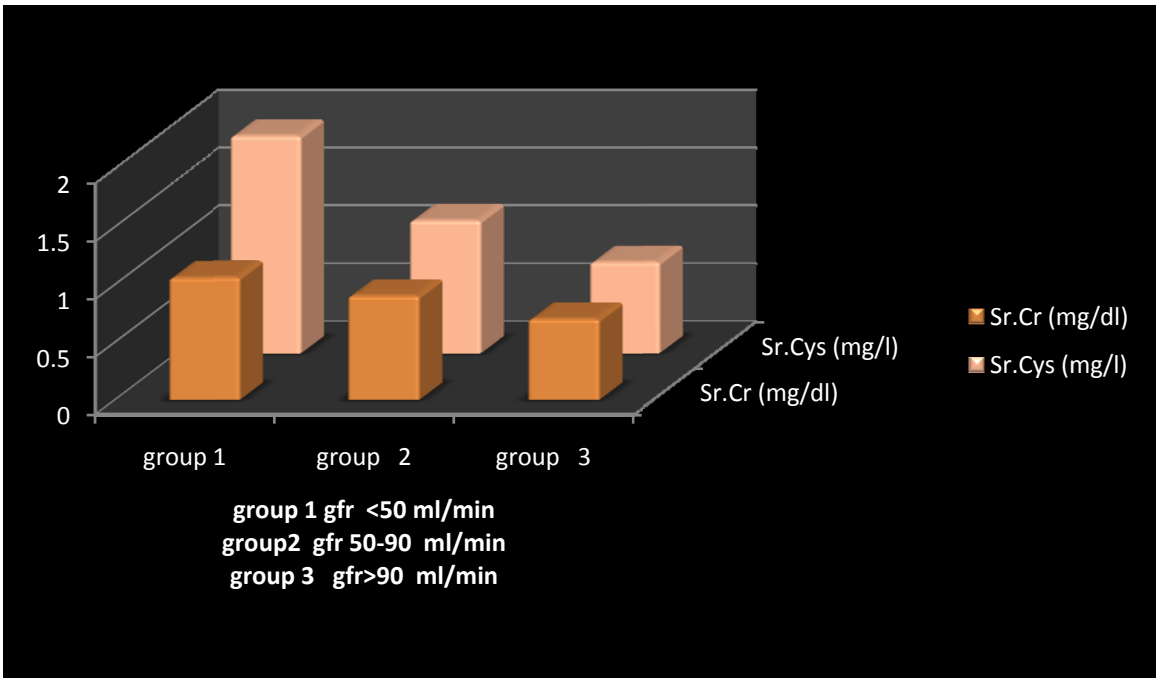
Child pugh score	GFR <50 ml/min	50-90 ml/min	>90 ml/min
A	02	10	04
B	08	11	02
C	10	03	00

Only two patients (12.5%) in Child Pugh A had GFR less than 50 ml/minute where as 10 (76%) patients out of thirteen in Child Pugh C had GFR < 50 ml/minute. Four (25%) out of sixteen patients had GFR >90 ml/minute where as none of the patients in Child Pugh C had GFR >90 ml/minute when cystatin C is used.

COMPARISON OF SERUM CREATININE AND SERUM CYSTATIN WITH GFR:

The mean serum cystatin and serum creatinine values across varying groups of GFR is as follows.

Chart no 10:



The mean serum creatinine when GFR was less than 50ml/min was 1.06 mg/dl whereas the mean serum cystatin C level was 1.88 mg/L. Serum cystatin C was found to be elevated from their normal levels where as serum creatinine levels were normal in patients with reduced GFR.

GFR BY MEASURED CREATININE CLEARANCE:

GFR measured by timed 24 hour urine collections and 24 hour urinary creatinine across various grades of Child Pugh are as follows

Chart no 11:

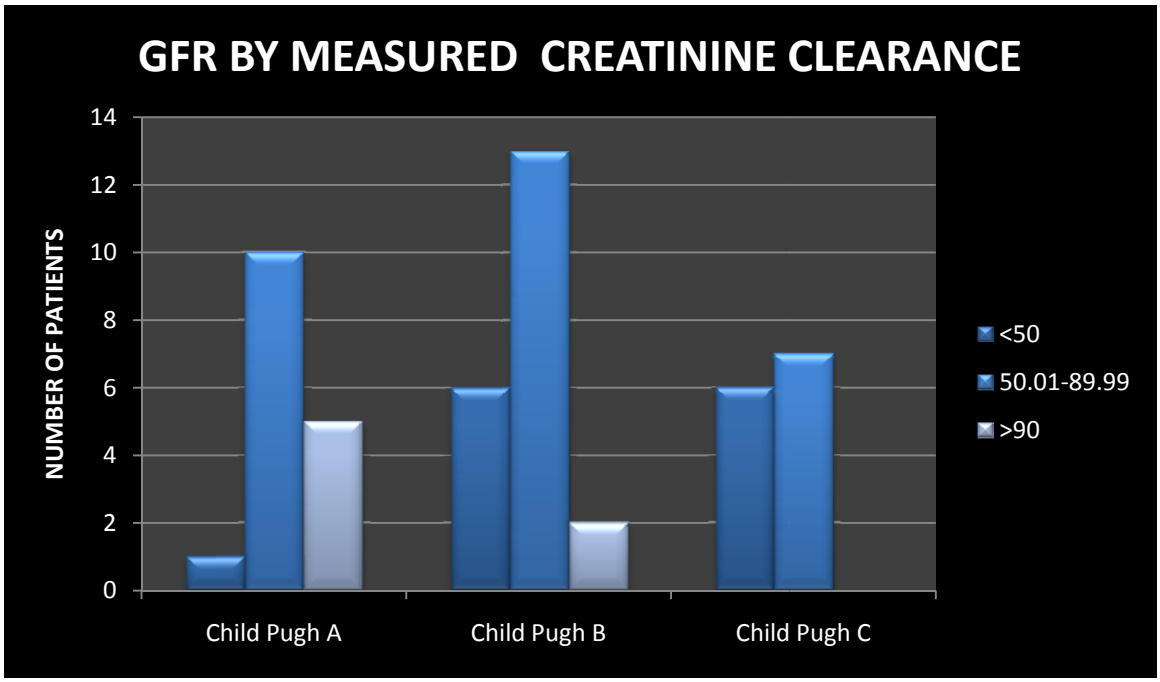


Table no 12:

Child pugh score	GFR <50 ml/min	50-90 ml/min	>90 ml/min
A	01	10	05
B	06	13	02
C	06	07	00

Only one patient (6.25%) in Child Pugh A had GFR <50 ml/minute where as six patients (46 %) in Child Pugh C had GFR <50 ml/minute when creatinine clearance is measured.

COMPARISON OF GFR BY VARIOUS METHODS:

The patients were grouped under three Categories. Group 1 included patients with GFR <50 ml/min according to Hoek's formula. Group 2 included those with GFR between 50 to 90 ml/min. Group 3 included those with GFR above 90 ml/min.

Chart no 12:

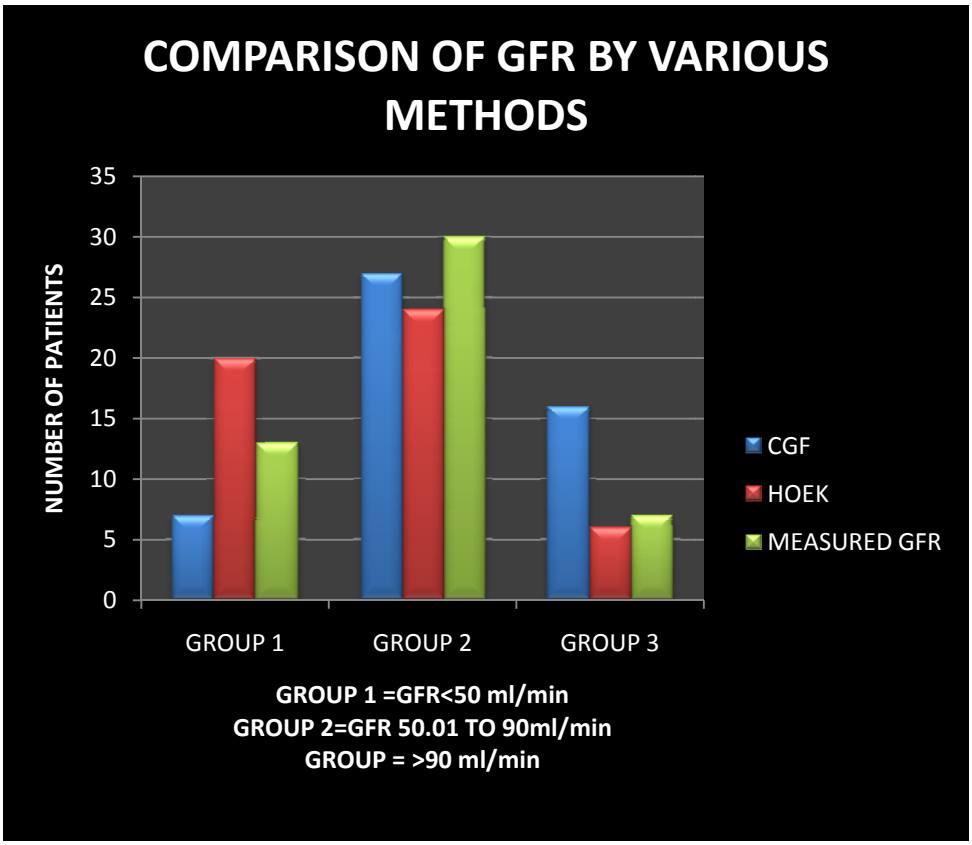


Table no 13:

METHODS	GROUP I (<50 ML/MIN)		GROUP II (50-90 ML/MIN)		GROUP III (>90 ML/MIN)	
COCKCROFT GAULT	07	(14%)	27	(54%)	16	(32%)
HOEK'S METHOD	20	(40%)	24	(48%)	06	(12%)
MEASURED CREATININE CLEARANCE	13	(26%)	30	(60%)	07	(14%)

On comparing GFR values obtained by the three methods, only seven(14%) out of fifty patients had GFR 50 ml/min by CGF, whereas 20(40%) was found to have GFR <50 ml/min when cystatin based formula is used. 13 (26%) subjects fell under group I when creatinine clearance was measured..

This shows that cystatin C based equations have better sensitivity in identifying small decline in glomerular filtration rate when compared to other methods.

Table no 14:

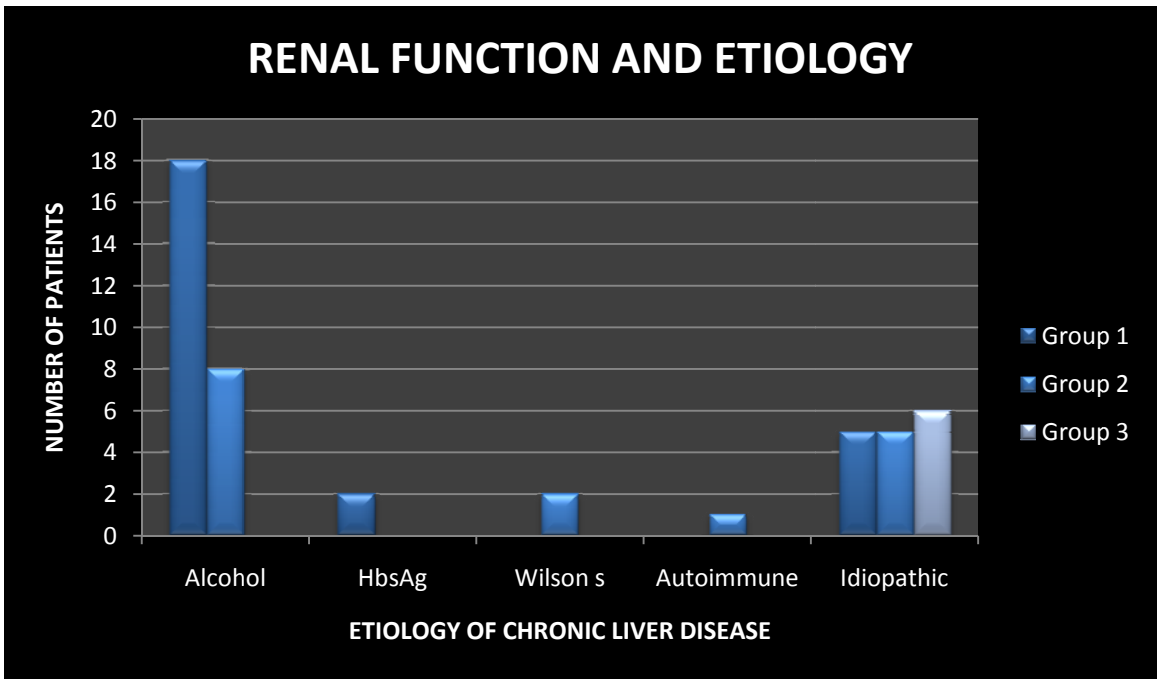
Methods	**Mean**	**SD**	**ANOVA 'F'**	**Sig.**	**Significantly differed Measures**
CGF	76.3	20.7	7.060	P<0.001	CGF& Hoek
Hoak	54.4	21.1			CGF& Mea GFR
Measured GFR	65.3	22.9			Hoek and measured GFR

The above table compares the CGF, Hoek and measured GFR. The mean of CGF was 76 ± 20.7, which significantly differed with other methods namely Hoek (54 ± 21.1) and measured GFR (65.3 ± 22.9) . P value was found to be < 0.001 which is significant.

The difference between Hoek procedure and measured GFR was statistically significant ($p < 0.05$)

RENAL FUNCTION AND ETIOLOGY:

The study subjects were grouped into three categories according to their GFR. Group 1 with GFR less than 50 ml/min, Group 2 with GFR between 50 to 90 ml/min and those with GFR more than 90 ml/min fall under Group 3.The GFR was compared in subjects with chronic liver disease due to various etiologies.



Out of 26 alcoholics, eighteen subjects (69.23%) had GFR less than 50 ml/min , and the eight (34. 78) had GFR in the range between 50-90 ml/min and none of them had GFR above 90 ml/min.

Of the six patients who are HbsAg positive only two (33.33%) had GFR less than 50 ml/min ,where as four patients (66.66%) had GFR above 50 ml/min.

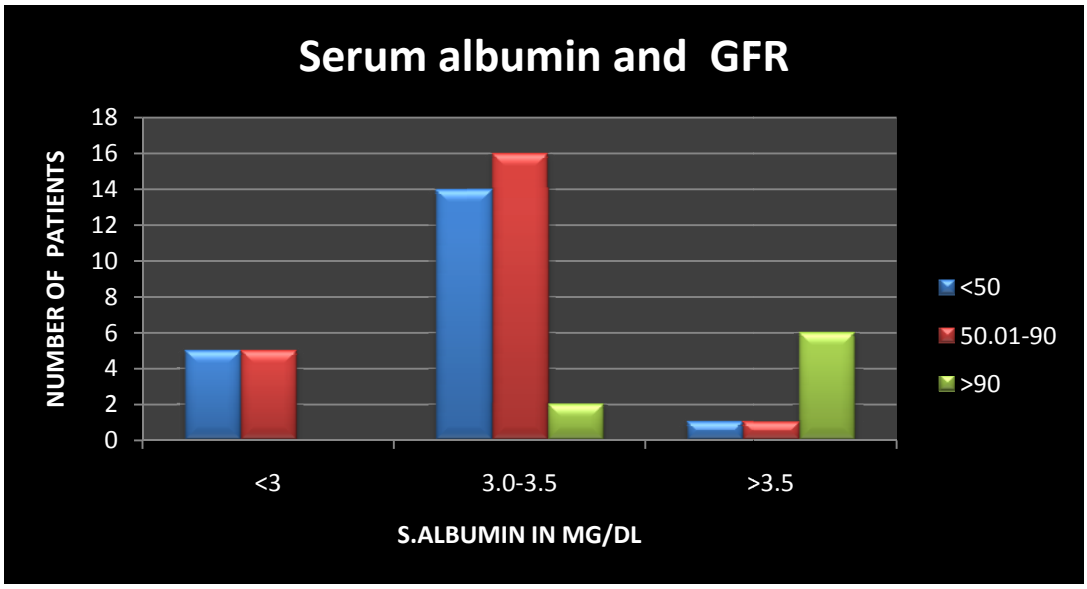
Chronic liver disease associated with Wilson's disease had GFR above 50 ml/min.

SERUM ALBUMIN AND RENAL FUNCTION:

Our study group was divided into three categories based on their GFR and serum albumin level distribution in all the three groups were noted.

Table no 15:

S.Albumin(mg/dl)	**Group 1(GFR<50ml/min)**	**Group 2 (GFR50-90 ml/min)**	**Group 3(>90 ml/min)**
<3.0	05	05	00
3.0-3.5	14	16	02
>3.5	01	01	06



The mean serum albumin level of the patients in three groups are

Group I – 3.02 gm/dl

Group II -3.25 gm/dl

Group III - 3.51 gm/dl.

Patients with higher GFR had marginally higher albumin levels. But it was not found to be statistically significant. ($p>0.05$).

DISCUSSION

We analyzed the extent of renal dysfunction in 50 patients with chronic liver disease. Till now creatinine based equations for estimating glomerular filtration rate are the most commonly used methods.These have the advantage of being free of urine collection errors.

In our study, even in patients with glomerular filtration rate less than 50ml/min serum creatinine levels were found to be normal and failed to raise above the upper reference limits.

The study by McAulay et al [44] also reported similar findings that serum creatinine is a poor indicator of renal function in chronic liver disease and was found to be within normal limits, even when GFR has reduced significantly.

The study by Caregaro et al[45] showed that serum creatinine had only 18.5% sensitivity in detecting reduced renal reserve in patients with cirrhosis at risk of renal dysfunction.

Papadakis and Arieff[46] had also reported similar observations that use of serum creatinine solely as a marker of renal dysfunction is highly erroneous and leads to a spuriously good renal reserve in these patients.

This may be due to the fact that the steady state concentration of creatinine is low in cirrhotics. The various factors contributing to reduced serum creatinine levels include malnutrition and reduced muscle mass in these patients. Also the hepatic synthesis of creatine which is the precursor of creatinine is reduced by 40 to 50 % in these patients. Renal tubular secretion of creatinine also increases in these patients , which further decreases serum creatinine levels.

Our study also showed that creatinine clearance by Cockcroft – Gault formula overestimates GFR in chronic liver disease patients. This is in agreement with the study done by Skluzacek et al comparing Cockcroft Gault and MDRD based formulas with iodine 125-iothalamate clearance which has also shown that both CGF and MDRD are inaccurate and overestimate GFR.

The study by McAulay et al reported similar observations and also showed that among the creatinine based equations MDRD formula is a better method for estimating GFR. This takes into account the patient' s age, sex, race, serum creatinine , serum albumin and blood urea nitrogen levels.

This may be due to the fact that body weight is a numerator and serum creatinine is a denominator in Cockcroft Gault formula . Increased

body weight due to ascites and edema with reduced serum creatinine contributes to the falsely elevated GFR by this method.

In our study serum cystatin C was found to raise as the renal function deteriorates indicating that it could be a reliable marker for renal dysfunction in decompensated chronic liver disease patients. 40% of the patients in our study had GFR < 50 ml/min when cystatin based formulas were used compared to 14% when creatinine based Cockcroft Gault formula was used.

Our study is in accordance with that of the study by Poge[47] et al which was done to evaluate the diagnostic accuracy of cystatin based formulas namely Hoek and Larsson equations and it showed that there was a significant improvement in estimation of GFR with lower bias and higher precision than creatinine based formulas but none were as accurate as inulin clearance.

The study undertaken by Herget- Rosenthal [48] to identify the better method in detecting the occurrence of renal dysfunction between serum cystatin C and serum creatinine and , serum cystatin C detected ARF earlier than serum creatinine by 1.5 ± 6 days (Risk criteria) and 1.2 ± 0.9 days by injury criteria.

Our study is in agreement with the Rocco Orlando et al [49]. Their study showed that serum cystatin C had a good diagnostic sensitivity (88%) when compared to serum creatinine (23%) to detect renal dysfunction. in cirrhotic patients.

Newman et al [50] reported similar results that not only serum cystatin C is a better marker than serum creatinine and that it is more sensitive to detect smaller changes in GFR. In our study too serum cystatin proved to be better than other methods.

In a meta analyses by Vikas Dharnika et al[51], Cystatin C has got a greater correlation coefficient than creatinine and the correlation of GFR with the reciprocal of Cystatin C increases as the renal function deteriorates.

In our study measured creatinine clearance by timed urine collections was better than serum creatinine and estimated GFR by Cockcroft- Gault method but less accurate than cystatin based formulas.

The study by Proulx et al [52] showed that though Inulin clearance is the most accurate method for estimating renal function , it is practically impossible in resource limited settings and though calculated

GFR by timed urine collection methods overestimates true GFR it is preferable to that of Cockcroft Gault formula.

The overestimation of true GFR may be due to the fact that there is increased tubular secretion in the setting of lower glomerular filtration leading to falsely high values of glomerular filtration rate.

The study by Papadakis .and Arrief and another study by Caregaro et al have supported this observation by concluding that calculated creatinine clearance may be an aid to true GFR in the absence of Inulin clearance.In our study there was no statistically significant correlation between the levels of serum albumin and renal function.

This is in agreement with a study by Hampel et al[53] which also had reported that serum albumin levels did not correlate with degree of renal dysfunction and it was not considered to be a significant risk factor for the development of renal dysfunction.

Our study has also shown that patients with alcoholic cirrhosis had adverse renal function compared to those with Hb sAg positivity. 69.23% of alcoholics had GFR below 50 ml/min where as only 33.33% of HbsAg positive individuals had GFR <50 ml/min.

In our study blood urea levels were found to be normal even when GFR was grossly reduced . This may be due to their reduced synthesis in patients with decreased hepatic function. Also they may falsely increase when there is gastrointestinal blood loss. Hence they are unreliable for assessing renal function in cirrhotics.

CONCLUSION

1) In patients with chronic liver disease ,plasma creatinine alone is a poor marker for detecting renal dysfunction.

2) Creatinine based Cockcroft- Gault formula grossly overestimates renal function.

3) Serum Cystatin C and cystatin C based formulas for estimating GFR is a better marker of renal dysfunction compared to serum creatinine and hence should be used for assessing renal function for making necessary dose adjustments in these patients.

4) Measured creatinine clearance though not accurate as cystatin C based formulas is better than Cockcroft Gault method.

5) Alcoholics develop severe renal dysfunction compared to patients with cirrhosis due to other causes.

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PROFORMA

NAME:

AGE:

SEX:

BODY WEIGHT (KG):

CAUSES OF CIRRHOSIS :

ALCOHOL	HEPATITIS -B	HEPATITIS -C	WILSON' S	AUTOIMMUNE

PRESENTING COMPLAINTS:

DURATION:

HISTORY:

1)FEVER

2)DIARRHOEA

3)VOMITING

4) ABDOMINAL PAIN

5) RAPID PROGRESSION OF ASCITES

6) GASTROINTESTINAL BLEED-

MELENA/HEMATEMESIS

7) GUM BLEED

8)DRUG HISTORY - DIURETICS/ANTIBIOTICS/RADIOCONTRAST AGENTS

CLINICAL EXAMINATION:

1) GENERAL CONDITION
2) PALLOR
3) JAUNDICE
4) SIGNS OF LIVER CELL FAILURE
5) BLEEDING TENDENCIES
6) ABDOMINAL DISTENSION
7) UGI BLEED
8) PEDAL EDEMA
9) OLIGURIA
10)VITALS- PULSE/BP/RESPIRATORY RATE/TEMPERATURE
11) ASCITES
12) LIVER SIZE
13) SPLENOMEGALY
14) SENSORIUM

LAB INVESTIGATIONS:

THYROID PROFILE LIVER FUNCTION TESTS:

SERUM BILIRUBIN:

TOTAL PROTEIN:

SERUM ALBUMIN:

SERUM GLOBULIN:

ASPARTATE AMINOTRANSFERASE(AST):

ALANINE AMINOTRANSFERASE (ALT):

AST/ALT RATIO:

PROTHROMBIN TIME:

BLOOD UREA:

SERUM CREATININE:

SERUM ELECTROLYTES:

URINE ANALYSIS:

URINE- ALBUMIN

DEPOSITS

24 HOUR URINE VOLUME:

24 HOUR URINE CREATININE:

SERUM CYSTATIN C:

HBsAG- POSITIVE/NEGATIVE

ANTI HCV ANTIBODY

ULTRASOUND ABDOMEN:

LIVER: SIZE IN CENTIMETER/ECHO TEXTURE

ASCITES- NIL/MODERATE/MASSIVE

SPLEEN-SIZE/COLLATERALS

PORTAL VEIN DIAMETER

KIDNEYS-SIZE/ECHO TEXTURE/CORTICO MEDULLARY

DIFFERENTIATION.

MASTER CHART

s.no	name	age	sex	b.wt(kg)	Cause	s.br	S.alb	Asc	PT(Sec)	H.enc	Childpugh	Bl ur	S.Cr	Egfr(CGF)	s.cys(mg/L	Egfr(Hoek)	24 hr U Vol	24 . cr	mea GFR
1	Isakki	36	m	54	Alc	4.2	2.9	e.con	13	min	10 (C)	20	0.8	97.5	0.995	76.43	1900	54	89.06
2	Thangam	27	f	48	Idio	2.8	4.2	none	13	nil	6 (A)	28	0.8	80.04	0.9	84.92	2100	49.5	90.23
3	Mari	36	f	50	Auto	10.2	3.7	e.con	16	min	9 (B)	36	0.9	68.2	1.33	57.45	1100	79.1	67.62
4	Jameela	26	f	42	Wil	3.8	3.4	e.con	23	min	12 (C)	48	1.1	51.39	1.5	51.11	990	83.6	52.29
5	Baskaran	45	m	78	Alc	10.6	3.1	e.con	13	nil	9 (B)	34	1.1	93.56	1.4	53.07	1590	97.6	97.6
6	Fathima	38	f	50	HbsAg	3	4	none	12	nil	6 (A)	28	0.6	100.34	0.73	105.74	2300	65	103.8
7	Irulandi	50	m	67	Idio	1.7	3.2	none	13	nil	6 (A)	22	0.8	93	1	76.03	2000	55	84.88
8	Sankaran	40	m	64	Idio	1.2	3.5	none	14	nil	6 (A)	28	0.8	111.11	0.82	93.66	1100	102	97.3
9	Murugan	40	m	54	Alc	3.1	2.6	p.con	14	nil	11 (C)	33	0.8	93.75	1.15	65.54	1900	54	89
10	Ganesan	57	m	68	Alc	6.7	3.2	p.con	15	nil	10 (C)	33	0.8	97.98	1.51	48.89	1900	50	82.47
11	Palraj	47	m	75	Alc	4.3	2.4	p.con	15	nil	11 (C)	50	1.4	67.4	1.43	51.86	1800	72	65
12	Kandan	48	m	53	Alc	1.2	3.2	none	12	nil	6 (A)	28	1	67.72	1.54	47.85	1500	53.99	55.99
13	Selvam	40	m	49	Alc	1.5	3.4	none	14	nil	6 (A)	18	0.8	85.06	0.9	84.9	1500	46	59.9
14	Kesavan	45	m	47	Idio	1.4	3.2	none	14	nil	6 (A)	26	1.2	51.67	1.23	60.97	1400	66	53.5
15	Elango	50	m	60	Alc	3.2	3.4	p.con	16	min	11 (C)	26	0.9	83.33	1.5	49.29	1400	46.25	49.96
16	Kalaiselvi	38	m	45	HbsAg	2.6	3.4	none	15	nil	7 (B)	28	0.8	67.73	1.44	51.47	1300	44	49.65

17	Sumathy	55	m	50	Idio	1.2	3.2	e.con	12	nil	7	(B)	22	1.2	41.81	1.62	45.27	1000	55	31.83
18	Sivagami	50	m	54	Idio	2.3	3.2	e.con	12	nil	8	(B)	22	1	59.01	1.64	44.67	1500	53.75	55.99
19	Palani	35	m	45	Idio	1.5	3.7	e.con	13	Nil	5	(A)	18	1	65.6	1.4	53.07	1250	64.5	55.99
20	Tamilan	51	m	53	Alc	16.4	3.4	e.con	15	min	8	(B)	43	1.4	46.79	2.6	26.58	850	43	18.13
21	John	38	m	48	Alc	1.2	3.3	e.con	15	nil	6	(A)	20	1	68	1.13	66.78	1250	64.5	55.9
22	Anbu	30	m	40	Alc	1.4	3.3	none	14	nil	6	(A)	22	1	61.11	1.8	40.31	1250	48	41.67
23	Murugan	42	m	46	Idio	1.7	3	e.con	13	nil	6	(A)	18	0.7	87.61	0.8	96.08	1119	61.25	68
24	Baalan	48	m	53	Alc	1.2	3.5	e.con	16	min	8	(B)	28	0.9	75.25	1.7	42.94	1400	46.25	49.96
25	Thangam	42	m	46	Idio	16.5	2.2	e.con	15.8	nil	7	(B)	16	0.7	89.44	1.2	62.63	1050	75.84	79
26	Muruges	42	m	50	Idio	1.4	3.1	none	12.4	nil	6	(A)	20	0.8	85.06	0.9	84.9	1900	50	82.47
27	Munusamy	40	m	60	Alc	1.2	3.7	e.con	13	nil	6	(A)	26	0.9	92.59	1	76.03	1950	60.7	92.59
28	Latha	40	f	44	Idio	2.7	1.8	e.con	14	nil	9	(B)	38	1.2	43.28	1.8	40.31	1100	58	36.92
29	Sankar	44	m	50	Alc	21.6	2.2	e.con	19.3	min	12	(C)	18	0.8	83.33	1.54	47.85	1700	53	78.21
30	Gandhi	44	m	45	Alc	20.6	4.6	e.con	27.7	min	11	(C)	31	0.9	68.57	1.51	48.89	1200	55	50.93
31	Selvam	40	m	52	HbsAg	0.8	3.3	none	13	nil	6	(A)	18	0.8	90.27	0.99	76.4	1900	50	82.47
32	Muniyan	45	m	69	Alc	3.1	3.2	e.con	16	nil	9	(B)	34	0.8	113.8	1.4	53.07	2100	49.5	90.23
33	Murugan	37	m	45	Alc	8.1	3	e.con	18	min	9	(B)	22	0.6	107.2	0.82	93.66	1300	55.82	84
34	Chellandi	54	m	46	Alc	5.8	4.3	e.con	14	nil	8	(B)	21	0.8	68.6	1.4	53.07	1500	46	59.9

35	Ibrahim	42	m	70	Idio	1.3	3.6	none	13	nil	5	(A)	26	1	95.2	0.8	96.08	2300	65	103.82
36	Narayan	58	m	54	Idio	2.7	3.2	e.con	18	nil	8	(B)	39	1	60	1.7	42.94	1900	52	68.6
37	Kuppan	42	m	50	Alc	3	3.5	none	14	nil	7	(B)	26	1	68.06	1.2	62.63	1900	52	68.6
38	Mari	40	m	56	Alc	3.3	3.3	p.con	12	min	11	(C)	40	1.2	64.81	1.8	40.31	1200	54.5	37.85
39	Sudalai	57	m	66	Idio	7.5	3.3	p.con	18	min	10	(C)	40	1.2	63.4	1.74	41.85	1000	55	31.83
40	Arumuga	58	m	60	Alc	2.8	3.3	e.con	15	min	8	(B)	34	1.1	62.12	1.8	40.31	990	83.7	52.29
41	Subbu	56	f	50	Alc	8	2.2	e.con	12	nil	10	(C)	39	1.1	45.05	2.56	27.06	1200	58.08	44
42	Sakthivel	35	m	44	Idio	2.2	3.2	none	13	nil	7	(B)	54	0.9	71.29	1	76.03	1100	79	67
43	Ravi	40	m	54	Alc	25.5	3	e.con	18	min	9	(B)	18	0.8	98.9	1.23	60.97	1900	54	89.06
44	Madhava	47	m	50	Alc	2.8	2	e.con	18	min	9	(B)	15	0.7	92.26	0.84	89.11	1050	75	77
45	Muruges	40	m	48	HbsAg	6	4	none	12	nil	7	(B)	24	0.6	111.11	0.82	93.66	1300	55	84
46	Selvi	56	f	50	HbsAg	6.2	2.3	e.con	14	nil	10	(C)	29	1.1	45.07	1.8	40.31	1200	58.08	44
47	Raja	38	m	49	HbsAg	1.2	4	e.con	12	nil	6	(A)	18	0.8	86.77	0.9	76	1700	53	77
48	Selvam	37	m	45	Wil	4	3.4	e.con	17	nil	9	(B)	30	0.8	107.22	1	76.03	1300	55	84
49	Isakki	24	m	34	Alc	1.8	3.1	e.con	20	min	10	(C)	20	1.2	45.55	2.6	26.58	400	48	11.11
50	Kandasamy	58	m	42	Alc	1	3	e.con	15	nil	7	(B)	24	1.2	39.86	3.1	21.56	800	50	23.15

Alc-alcohol, AI- autoimmune, idio-idiopathic, sr.br-serum bilirubin, sr.alb-serum albumin, asc-ascites, e.con- easily controlled, p.con-poorly controlled, h.enc-hepatic encephalopathy, min-minimal, adv-advanced. PT-prothrombin time, bl.ur-blood urea, sr.cr-serum creatinine, Egfr-estimated GFR, CGF-ockcroft gault formula, s.cys-serum cystatin, mea.gfr- measured GFR.